

## What is the best way to manage screening for infections and vaccination of inflammatory bowel disease patients?

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increased risk of opportunistic infections, in particular of viral or bacterial etiology. Despite the existence of international guidelines, many gastroenterologists have not adopted routine screening and vaccination in those patients with IBD, which are candidate for biologic therapy. Available strategies to screen, diagnose and prevent bacterial and viral infections in patients with IBD prior to start biological therapy are discussed in this review.

**Key words:** Inflammatory bowel disease; Opportunistic infections; Immunomodulators; Corticosteroids; Anti-tumor necrosis factor agents

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**Core tip:** The increasing use of biologics as a mainstay of therapy in inflammatory bowel disease (IBD) is associated with an increased risk for a variety of infections, many of which are preventable by prior screening and vaccination. While immunocompetent IBD patients can be vaccinated using standard vaccination schedule, special guidelines need to be followed for IBD patients getting immunosuppressive therapy (IST). This article provides a review of the issues surrounding immunizations in the IBD patient and a practical guide for clinicians regarding the appropriate screening for infections and vaccinations to administer both before and during IST.

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### Abstract

The use of biological agents and immunomodulators for inflammatory bowel disease (IBD) is associated with an

### INTRODUCTION

Biological agents have represented a breakthrough in the therapy of inflammatory bowel disease (IBD) in the last

20 years: Tumor necrosis factor alpha inhibitors (anti-TNF) and other monoclonal antibodies targeting interleukin 12 (IL-12), IL-23, and cellular adhesion molecule ligands  $\alpha 4$  integrin and  $\alpha 4\beta 7$  integrin. The European Crohn's and Colitis Foundation (ECCO) outlines that IBD patients treated with corticosteroids (prednisone 20 mg/d equivalent for 2 wk or more), immunomodulators (6-mercaptopurine, Azathioprine, Methotrexate), and biological agents should be considered immunocompromised and at risk for opportunistic infections<sup>[1]</sup>. This has been confirmed by several studies, highlighting the increased incidence of severe infections in patients with IBD on biologics<sup>[2,3]</sup>. A pivotal study in the field<sup>[4]</sup> has evaluated the independent predisposing factors to severe infections with a case-control designed study. The results underlined how immunosuppressive therapy (steroids, thiopurines, and anti-TNF) were associated with an increased risk of severe infections (OR: 2.9, 95%CI: 1.5-5), and that the risk was greatly increased when two or more drugs were combined (OR: 14.5, 95%CI: 4.9-43). The TREAT Registry (Crohn's Therapy, Resource, Evaluation, and Assessment Tool) has individuated prednisone, infliximab, disease activity (moderate to severe), and narcotic analgesic treatment as independent factors associated with serious infections<sup>[3]</sup>. A recent Cochrane review, with a meta-analysis of randomized controlled trials, controlled clinical trials, and open-label extension studies of biologics for several indications, reported an OR of 1.28 (95%CI: 1.09-1.50) for serious infections for patients on any biologic<sup>[5]</sup>. However, a subgroup analysis of patients included in IBD trials did not show a significantly increased risk of infection (OR: 1.28, 95%CI: 0.67-2.44)<sup>[4]</sup>. In this review, we aim to outline the most relevant opportunistic infections in IBD with focus on the discussion of the screening and prevention strategies through vaccination or chemoprophylaxis in IBD patients prior to start biological therapy.

## BACTERIAL DISEASES

### *Mycobacterium tuberculosis*

The worldwide incidence of tuberculosis (TB) has been estimated by the World Health Organization in 9.6 million cases with 1.5 million deaths in 2014<sup>[6]</sup>. The risk of reactivation of latent TB (LTB) is 5-fold increased in the first 52 wk. after initiation of anti-TNF therapy<sup>[7-9]</sup>.

TNF has a central role in the immune response to *Mycobacterium tuberculosis*. It is fundamental for macrophage activation and in the formation and maintenance of granuloma where mycobacteria are sequestered<sup>[7]</sup>. This is a main reason why therapy with anti-TNF agents can reactivate latent TB. Generally these cases are extra pulmonary or disseminated TB<sup>[10]</sup>. The American College of Gastroenterology and the American Gastroenterological Association, as well as the ECCO recommend screening for LTB before starting biological therapy<sup>[11-14]</sup>. The most commonly employed screening tests are tuberculin skin test (TST), QuantiFERON TB-Gold (QFT-G) and chest radiography. *In vitro* assays

based on interferon-gamma release (IGRA), such as the QFT-G and T-SPOT.TB, have been recently claimed to be more specific and sensitive than TST, particularly in the previously vaccinated and immunosuppressed population<sup>[9,15]</sup>. IGRAs employ antigens specific for *Mycobacterium tuberculosis*, not cross-reactive with Bacillus Calmette-Guérin (BCG). A meta-analysis<sup>[16]</sup> has calculated the specificity of QFT-G and TST for LTB screening. In subjects who had not been vaccinated with BCG, the specificity of QFT-G was 99% (95%CI: 98%-100%) and that of TST was 97% (95%CI: 95%-99%). However, in subjects vaccinated with BCG, the specificity of QFT-G was 96% (95%CI: 94%-98%) while that of TST was only 59% (95%CI: 46%-73%). A Swiss study has compared TST and QFT-G performances in IBD patients<sup>[17]</sup>. The studied population comprised 114 patients with Crohn's disease (CD), 44 with ulcerative colitis (UC), 10 with indeterminate colitis and 44 control subjects. In this study the prevalence of BCG vaccination was 71%, while 81% of the IBD patients were treated with immunosuppressive therapy (IST). Less patients treated with IST were TST positive compared to those not treated with IST (14% vs 34%,  $P = 0.007$ ), while no difference was evident for the interferon-based test QFT-G (9% vs 6%). The correlation of TST and QFT-G in IBD patients was negative in this study ( $k = -0.0297$ ,  $-0.0314$  in vaccinated and  $-0.0538$  in non-vaccinated patients). However the two tests showed a better agreement in control subjects ( $k = 0.13$ ), and particularly in non-vaccinated controls ( $k = 0.62$ ).

These results were confirmed by a study by Andrisani *et al.*<sup>[18]</sup> performed on 92 Italian IBD patients who underwent infectious disease screening before starting therapy with anti-TNF (only one of them was vaccinated with BCG). A discordant result between QFT-G and TST was found in 10.8% IBD patients ( $k = 0.508$ ). Patients treated with IST had higher degree of disagreement (14.3%,  $k = 0.39$ ), while the patients not treated with IST had a 100% conformity of the two tests. A systematic review and meta-analysis has evaluated the findings of IGRA tests<sup>[19]</sup> in IBD patients. In the nine selected studies, different results were found for the agreement between skin test and the different IGRAs. TST and QFT-TB Gold/QFT-TB Gold In-Tube had a rate of uniformity of 85% (95%CI: 77-90), while the conformity of TST and T-SPOT.TB was 72% (95%CI: 64-78). A relevant problem in interpreting these results is the occurrence of indeterminate test. In this meta-analysis it was 5% (95%CI: 2-9) for all QFT-tests. IST therapy affected both QFT-G scores (OR: 0.37, 95%CI: 0.16-0.87) and TST outcomes (OR: 0.28, 95%CI: 0.10-0.80) in these studies ( $P = 0.02$ ). Patients with LTB infection should be treated with a 9 mo. course of isoniazid. This prophylaxis should preferably be conducted in strict cooperation with infectious disease specialists and/or pneumologists. The usual isoniazid protocol is generally well tolerated. Although IBD patients may already be on pharmacological treatment, there is no evidence of an increased risk of liver toxicity related

to isoniazid<sup>[20]</sup>. Even if not formally assessed in clinical studies, there is general agreement that a minimum of 2 mo should be waited after start of chemoprophylaxis for LTb before anti-TNF therapy is initiated<sup>[7,15]</sup>, if the clinical condition of the patient allow this delay. However, chemoprophylaxis does not guarantee that LTb will not reactivate during anti-TNF therapy: A reactivation rate of 19% has been described in a retrospective study, indicating that routine TB surveillance during and after anti-TNF drugs treatment must be performed<sup>[21]</sup>.

### ***Clostridium difficile***

*Clostridium difficile* infection (CDI) manifests with laboratory signs and symptoms that may be confused with a relapse of inflammatory activity in an IBD patient<sup>[22]</sup>. For this reason, it is mandatory to perform specific diagnostic tests for CDI in IBD relapses characterized by profuse diarrhea, with or without the presence of blood, by signs of dehydration and leukocytosis. The most common tests employed for CDI diagnosis are enzyme-linked immunosorbent assay (ELISA) for toxin A and B<sup>[23]</sup> and polymerase chain reaction (PCR) assays (which have greater specificity and sensitivity). Although toxigenic culture can be considered as the "gold standard" technique for this diagnosis, it is infrequently performed<sup>[23]</sup>. According to the Infectious Disease Society of America (IDSA), a 2-step method should be used. As a first step, an ELISA for the *Clostridium difficile* common antigen, glutamate dehydrogenase is performed. If positive, the presence of pathogenic strains can be confirmed by other techniques as cell cytotoxicity assay or toxigenic culture<sup>[24]</sup>. Treatment includes initially oral metronidazole and oral vancomycin, or in severe cases simultaneous administration of intravenous metronidazole and oral vancomycin<sup>[25]</sup>. Fidaxomicin has been recently approved for CDI<sup>[26,27]</sup>. In recent years, a innovative methodology has demonstrated its efficacy for treatment of recurrent CDI: Fecal microbiota transplantation<sup>[28]</sup>. Although the donor selection criteria and the optimal condition for fecal instillation are still not clearly defined, the method is widely and successfully employed<sup>[29]</sup>. FMT has been employed also for IBD patients with CDI in a recent study<sup>[30]</sup> using standardized frozen preparation, showing efficacy in treating the infection.

### ***Streptococcus pneumoniae***

*Pneumococcus* may cause, besides lung infection, also invasive disease as bacteremia and meningitis. Immunocompromised hosts are at risk for these complications, and cases have been described in IBD patients treated with infliximab<sup>[31]</sup>. Vaccination is recommended for prevention of pneumococcal infections in special at risk populations. The main risk categories applicable to IBD patients are age 65 years and older, smoking and use of immunosuppressive agents. Two vaccines have been approved against pneumococcal infections: A 23-valent-polysaccharide vaccine (PPSV23) and a 13-valent conjugate vaccines (PCV13). The coverage

of the two vaccines is only partly overlapping. The Advisory Committee on Immunization Practices (ACIP) guideline have been released with differential indications for different age and disease groups. In particular, ACIP suggests the following vaccination scheme for immunocompromised adults aged 19 years or older: If naïve to pneumococcal vaccine, they should receive first PCV13 and, at least 8 wk later, a shot of PPSV23<sup>[32]</sup>. Those subjects who had previously been vaccinated with PPSV23 should receive, at least one year later, an injection of PCV13<sup>[33]</sup>. While data concerning the need for revaccination with conjugated vaccine are scant, PPSV23 revaccination after 5 years is recommended for immunocompromised patients<sup>[34]</sup>. However, the response to *Streptococcus pneumoniae* vaccinations may be impaired in IBD patients treated with immunomodulators, particularly when they are used in combination<sup>[35,36]</sup>. For this reason, it would be advisable to perform vaccinations for pneumococcal infections before starting immunosuppressive drugs. Pneumococcal infections can usually be diagnosed by cultures or by search for urine antigens of *Streptococcus pneumoniae*. While pneumonia is generally treated with success with fluorquinolones, treatment of meningitis should rely on isolation of the organism and *in vitro* susceptibility testing<sup>[37]</sup>.

## **VIRAL DISEASES**

### ***Hepatitis B virus***

The prevalence of hepatitis B virus (HBV) in patients with IBD is similar to that of the general population<sup>[38]</sup>. The risk for hepatitis B reactivation has been clarified in a multicenter study<sup>[38]</sup> of 2076 Spanish IBD patients. This study has shown a lower prevalence of HBV antigens and/or antibodies than previously reported, and not different from control population. The HBV surface antigen (HBsAg) was present in no more than 1% of IBD patients, while the positivity rates for anti antibodies against the HBV core antigen (HBcAb) were 7.1% for CD and 8% for UC. A French study<sup>[39]</sup> showed similar results, with a prevalence of HBcAb of 2.78% in CD patients and of 1.59% in UC patients, not different from those detected in the control unselected population. Other studies<sup>[40-42]</sup> have shown in IBD patients a higher prevalence of HBV infection. Two Italian studies have reported somehow different results: Biancone *et al*<sup>[41]</sup> described a higher prevalence of HBcAb in CD and UC patients (10.9% and 11.5%, respectively), when compared to controls (5.1%,  $P < 0.02$ ). Papa *et al*<sup>[43]</sup> reported that only one patient out of 301 (0.3%) was an HBsAg carrier, while 22 (7.3%) were anti-HBc positive.

TNF- $\alpha$  is important in regulating hepatitis B replication<sup>[44]</sup> and cases of reactivation of the virus under TNF inhibitors have been published<sup>[45,46]</sup>. All IBD patients should be tested for HBV infection (HBsAg, anti-HBs, anti-HBc) to assess infection or vaccination status. It is important to check also for anti core antibodies, as

they could represent the only positive test in particular situations, such as the case of immunosuppressed patients or hepatitis C virus (HCV)/human immunodeficiency virus (HIV) co-infections<sup>[47]</sup>. However, a low rate of false positivity has been described. In patients that show positive findings of HBV infection, the search of HBeAg, anti HBe, and HBV DNA should also be performed.

Cases of reactivation on Infliximab therapy have been described not only in hepatitis B surface antigen (HBsAg)-positive patients but also in HBsAg-negative/anti-HBc (hepatitis B core antigen)-positive patients<sup>[48]</sup>. Hepatitis B reactivation is associated with significant morbidity and mortality due to hepatic failure<sup>[49]</sup>.

During anti-TNF therapy, "occult" HBV carriers (those who are anti-HBc+), need a frequent check of tests of liver function and of HBV markers: The appearance of HBV-DNA or HBsAg positivity indicates reactivation of the infection<sup>[1]</sup>. In chronic HBsAg-positive carriers, antiviral prophylaxis is recommended before administering immunosuppressive agents. If IST is anticipated to be conducted for a period of more than one year (as frequently happens in IBD), prophylaxis of HBV reactivation should be performed with nucleotide/nucleoside analogues rather than with lamivudine due to the lower incidence of mutations that generate resistance to the drug<sup>[1]</sup>. The American Association for the Study of Liver Diseases (AASLD)<sup>[50]</sup> and the European Association for the Study of the Liver recommend the early introduction of nucleoside/nucleotide analogues (NAs) for all HBsAg-positive patients requiring IST. Prophylaxis of HBV reactivation must be started at least one week before IST and it should last for 6 mo to 1 year after its accomplishment, because the reactivation of HBV may happen even after immunosuppression is withdrawn<sup>[50,51]</sup>.

Patients with high levels of HBV DNA (> 2000 IU/mL) at baseline should carry on the antiviral therapy until the same end points as for non-immunosuppressed patients are reached.

All seronegative (negative or low-titer HBsAb) patients should be vaccinated at diagnosis; however, this occurs in less than half of the patients<sup>[52]</sup>. It is safe to administer the standard vaccination protocol to patients with IBD on immunosuppressive medications, but the response may be significantly reduced, and an intensified vaccination protocol may be required. Post-vaccination HBsAb titers should be monitored, and, if non-protective (< 10 mU/mL), a booster dose or revaccination should be administered<sup>[47]</sup>. HBV vaccination seems not to be very common in IBD patients, according to four studies exploring the topic. Positive anti-HBs and negative HBcAb, as indication of efficacious vaccination was detected in only 12%, 48.9%, 24% and 21.7% of the four patients cohorts from Spain, Italy, France and China, respectively<sup>[38,43,53,54]</sup>. Vaccination programs are significantly different across Europe for what concerns period of initiation of the programs age and target population (newborns, adolescent and pre-adolescent

subjects, only for high-risk groups, etc.)<sup>[55]</sup>. For these reasons, it is recommended to determine of the infectious or vaccination status at the time of the first diagnosis of IBD. If possible, seronegative subjects (HBsAg, HBcAb and HBsAb negative) should be vaccinated as soon as possible in order to reduce future problems in management.

### HCV

The prevalence of HCV in patients with IBD is similar to that of the general population<sup>[38]</sup>. There are no data to suggest that biologics are associated with reactivation or exacerbation of the course of HCV<sup>[56,57]</sup>. Anti-TNF medications are generally considered safe in patients with HCV<sup>[43,58]</sup>. The prevalence of HCV infections in IBD patients has been recently evaluated in studies performed in Italy<sup>[41,43]</sup>, France<sup>[53]</sup>, Spain<sup>[38]</sup>, and China<sup>[54]</sup>. From these reports, the prevalence of hepatitis C infection in IBD patients seems to be not different from the general population. Biancone *et al*<sup>[41]</sup> reported that the prevalence of anti-HCV antibody positive individuals was 7.4% in CD patients, 0.6% in UC patients and 5.1% in the controls. The ECCO guideline<sup>[1]</sup> suggest to perform HCV screening before starting treatment with immunosuppressive drugs for IBD, although the positivity of HCV testing is not a contra-indication for IST. Testing should be performed by search for anti-HCV antibodies and, if antibodies are positive, by HCV-RNA. In case of positivity, these tests should be repeated periodically during immunosuppressive treatment. Prophylactic treatment is currently not available to prevent reactivation of HCV infection. Interferon, which was the milestone of antiviral therapy for HCV until the advent of direct-acting antiviral agents, is contraindicated in IBD forms that require IST.

### Cytomegalovirus

Cytomegalovirus (CMV) infection or reactivation can occur in patients with immunosuppressive conditions. CMV may produce retinitis, pneumonia, encephalitis, and other invasive infections<sup>[59]</sup>. A number of studies have described an association between severe steroid-refractory IBD and CMV infection<sup>[60,61]</sup>. Colonic CMV disease was observed in steroid-refractory UC (active), with a prevalence of 32%<sup>[60]</sup> in a prospective case-control report. There is no CMV vaccine available. Histopathology combined with immunohistochemistry (IHC) is specific and sensitive for detecting CMV infection in tissue or biopsies. PCR for CMV DNA is commonly employed both in blood and in biopsies to confirm the diagnosis. Screening for CMV infection is not necessary before starting immunomodulator therapy<sup>[14]</sup>. When CMV is detected in the intestinal mucosa of patients with severe steroid-resistant colitis treated with immunomodulators therapy, antiviral therapy should be initiated. The discontinuation of immunomodulators should be considered until symptoms of colitis ameliorate or in case of systemic CMV disease.



**Varicella zoster virus**

Varicella zoster virus (VZV) can be associated with a significant morbidity and mortality in immunocompromised patients. VZV is an herpes viruses that persists after acute infection in a latent state in autonomic ganglia, dorsal nerve roots, and cranial nerves<sup>[62]</sup>. Later in life it can reactivate as zoster. In addition to clinical signs, that are generally typical, PCR for VZV or fluorescence testing can be performed on biological material such as vesicular fluid, sputum, and cerebrospinal fluid. A four-fold or greater rise in VZV antibody titer in acute and late serum specimens is diagnostic of VZV infection<sup>[63]</sup>. The increased risk of VZV reactivation is not specific only to biologics. In a recent large cohort study<sup>[64]</sup> including more than 33000 patients treated with anti-TNF medications and 27000 control individuals treated with non-biological anti-inflammatory medications for various indications (3850 patients with IBD), the risk of herpes zoster was similar in patients with IBD treated with anti-TNF agents and with thiopurines.

VZV-related complications can be easily prevented by vaccination. However, live vaccine for varicella must not be administered to patients on immunosuppressive therapies<sup>[65]</sup>, including azathioprine, methotrexate, 6-mercaptopurine, and infliximab<sup>[66]</sup>. In this regard, it should be noted that Lu *et al*<sup>[67]</sup> have described good tolerance for VZV vaccine in six patients with IBD receiving immunosuppressive drugs (6-MP or infliximab). Prospective studies are needed to delineate the risks and benefits of live varicella vaccine in patients with IBD. Probably, the better behavior should be to test for VZV patients as early as possible after diagnosis and to vaccinate those previously unexposed before prescribing immunosuppressive treatments. Recently, the use of a zoster vaccine has been suggested for patients who are VZV positive and at risk of developing herpes zoster (*e.g.*, the elderly). Currently, guidelines suggest a lag time before the varicella and zoster vaccine and the start of immunosuppression of 14 d to 1 mo<sup>[68,69]</sup>. The vaccine should not be administered for at least 1 mo. after the cessation of immunosuppression<sup>[68,69]</sup>. A study of zoster vaccine given to patients on biologics has detected, however, no association with short-term increase in herpes zoster incidence. In the meantime, it was associated with a lower herpes zoster incidence at a follow-up of two years (6.7 vs 11.6 cases per 1000 person-years;  $P < 0.001$ )<sup>[70]</sup>. For those patients with IBD which are VZV seronegative and treated with immunosuppressive drugs, who experience exposure to subjects with active VZV infection, passive immunization with high-dose VZV IgG<sup>[69]</sup> should be considered.

**HIV**

All IBD patients undergoing IST should receive testing for HIV infection (by search of HIV p24 antigen and antibody, and, if acute infection is suspected, by PCR) to exclude unidentified infection. This should be done in order to avoid possible adverse outcomes of immunosuppressive

drugs in HIV infected subjects<sup>[1]</sup>. Several case series and case reports describing patients who are infected with HIV and were treated with anti-TNF medications for various indications have been published and all the patients who were submitted to therapy had a satisfactory CD4 cells count, no co-infection, and low HIV viral load<sup>[71]</sup>. However, because there are limited data on the effect of treatment with HAART on the course of concomitant HIV and IBD, no recommendations are available<sup>[1]</sup>. Nevertheless, HIV infection is not to be considered a contra-indication to anti-TNF therapy.

**Human papillomavirus**

Human papillomavirus (HPV) is a sexually transmitted infection. It is a common infection and is the causative agent for cervical cancer and premalignant conditions<sup>[72,73]</sup>. The American College of Obstetricians and Gynecologists guideline requires to initiate screening for cervical cancer at 21 years of age, independently of the age of beginning of sexual activity<sup>[74]</sup>. There are some studies that have suggested how women with IBD could have a higher incidence of cervical dysplasia<sup>[75,76]</sup>. There is an increased incidence of HPV-associated warts or condylomata in patients taking immunosuppressants; however, no data suggesting a specific association with biologics are available<sup>[77]</sup>. Women affected by IBD should have cervical smears and HPV vaccination according to the general population guidelines<sup>[74]</sup>. The available vaccine is quadrivalent, and it is given as three doses during a period of 6 mo. The vaccine is indicated for women of the age of 9 to 26 years, both before and after initiation of sexual activity<sup>[75]</sup>. HPV vaccine is also recommended for young males, with vaccination at the age of 11 to 12 years, and catch-up for those aged 13 to 21 years. However, vaccination policies are diverse in different countries. Therapy of eventual abnormal findings at cervical smears includes colposcopic examination, and surgical excision.

**Herpes simplex virus**

In immunocompromised patients, herpes simplex virus (HSV) infection may cause severe disseminate infection of different organs (including encephalitis, meningitis, pneumonia, gastrointestinal infection, and hepatitis)<sup>[78,79]</sup>. Diagnosis of HSV infection is generally suspected based on clinical findings. It can be confirmed by cytology, by PCR, and by search for specific circulating immunoglobulin G (IgG) and IgM. IBD guidelines from the ECCO dissuade to start IST during when an HSV infection is ongoing<sup>[1]</sup>. Only those immunosuppressed patients who manifest recurrent infection from HSV type 1 or 2 should receive specific chemoprophylaxis<sup>[80]</sup>.

**Epstein-Barr virus**

Epstein-Barr virus (EBV) is a common B-cell lymphotropic gamma-herpes virus infection in humans. Most of the severe EBV diseases, as hemophagocytic lymphohistiocytosis, occur when primary infection happens in immunosuppressed patients; for this reason it is

**Table 1 Screening and vaccinations for inflammatory bowel disease patients prior to start immunosuppressive including anti-tumor necrosis factor therapy**

Infection	Tests	Recommended screening	Vaccine
TB	LTB should be tested by a combination of patient history, chest X-ray, TST and QFT-G	Yes	Always contraindicated during immunosuppressive therapy and in children exposed in utero to anti-TNF, up to 6 mo of age, like any other live vaccine
<i>Clostridium difficile</i>	Enzyme immunoassay Against toxin A and B and PCR assays	Not necessary	Not available
<i>S. Pneumonia</i>	Culture of relevant clinical samples (blood, CSF, good respiratory sample), urine	Not necessary	Yes
HBV	Blood test for HBsAg, anti-HBsAb and HBcAb to determine HBV status. In patients with positive HBsAg, viremia HBV-DNA should also be quantified	Yes	Recommended standard or double dose schedule
HCV	HCV serology	Yes	Not available
CMV	CMV serology	No	Not available
HIV	Blood test for HIV serology	Yes	Not available
VZV	VZV serology	Yes	Vaccine available, vaccinate before starting immune suppressants
HPV	Cervical cytology	Yes	Recommended
HSV	HSV serology	Not necessary	Not available
EBV	EBV serology	Advisable	Not available
Influenza virus	clinical signs and laboratory evaluation	Not necessary	Recommended

TNF: Tumor necrosis factor; TB: Tuberculosis; LTb: Latent tuberculosis; TST: Tuberculin skin test; QFT-G: Quanti FERON TB-Gold; PCR: Polymerase chain reaction; CSF: Cerebrospinal fluid; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CMV: Cytomegalovirus; HIV: Human immunodeficiency virus; VZV: Varicella zoster virus; HPV: Human papillomavirus; HSV: Herpes simplex virus; EBV: Epstein-Barr virus.

**Table 2 Vaccination of inflammatory bowel disease patients on immunosuppressive therapy**

Vaccine	Dose	Safety
Inactivated vaccines		
HAV	2 doses	Yes
HBV	3 doses	Yes
HAV and HBV	3 doses	Yes
HPV	3 doses	Yes
Influenza (trivalent)	Annually	Yes
Meningococcal	≥ 1 dose	Yes
Pneumococcal	1 dose and 1 booster in 5 yr	yes
Tetanus and diphtheria	Every 10 yr	Yes
Live attenuated vaccines		
BCG	1 dose	Contraindicated
MMR	1 or 2 doses	Contraindicated
Varicella	2 doses	Contraindicated
Zoster	1 doses	Contraindicated

HAV: Hepatitis A virus; HBV: Hepatitis B virus; HPV: Human papillomavirus; BCG: Bacillus Calmette Guérin; MMR: Measles, mumps, and rubella.

advisable to test IBD patients for EBV serology before start biological or immunosuppressive therapy<sup>[81]</sup>. EBV-associated lymphomas have been described in patients with CD treated with 6-MP or azathioprine<sup>[82,83]</sup>. An observational cohort study was conducted in France, the CESAME (Cancers et Surrisque Associe aux Maladies inflammatoires intestinales En France) study. In this IBD cohort the incidence of lymphoproliferative diseases was evaluated according to the treatment with thiopurines during a period of 3 years. This research described how

the risk of lymphoproliferative diseases is increased in thiopurine users with a hazard ratio of 5.28 (95%CI: 2.01-13.9,  $P = 0.001$ )<sup>[84]</sup>. Two types of thiopurine-induced lymphoma in IBD are EBV-related: the post-transplant-like lymphoma that develops in adult patients seropositive for EBV and a fatal early post-mononucleosis lymphoproliferation that may develop in young men (< 35 years) seronegative for EBV<sup>[85,86]</sup>. While antiviral drugs have no beneficial effect on EBV-induced B-cell proliferation, rituximab is the drug of choice for treating established B-cell lymphoma<sup>[87]</sup>. Screening for EBV infection before initiation of immunomodulator therapy should be considered. Anti-TNF monotherapy could be used in preference to thiopurines in EBV seronegative patients at the clinician’s discretion<sup>[61]</sup>. No EBV vaccine is available.

**Influenza virus**

Influenza viruses A and B cause seasonal epidemics. In healthy subjects who are immunocompetent, influenza usually behaves as an acute, self-limiting illness of upper respiratory tract. Patients on IST, including patients with IBD on IST, are considered to be at high risk for complications: Viral and bacterial pneumonia, acute respiratory distress syndrome, encephalopathy, myocarditis, pericarditis, and myositis<sup>[1]</sup>. The diagnosis of influenza is made a combination of typical clinical signs and of laboratory tests. The gold standard for diagnosis is PCR testing from respiratory specimens<sup>[88]</sup>. The most effective way to prevent influenza and its complications is vaccination. The vaccine approved for use in individuals older than 6 mo of age, including immunosuppressed

patients is the injectable inactivated trivalent vaccine<sup>[89]</sup>. Vaccination against influenza with inactivated vaccines is recommended for (IBD) patients according to published guidelines both in the US and Europe. Some studies have suggested quantitatively reduced response to influenza vaccine in IBD patients on combined immunosuppression<sup>[90]</sup>. However, due to the lack of specific data, there is not a current recommendation for a repeated dose of vaccine or for checking serological response after vaccination in these patients<sup>[1]</sup>. Based on the currently available data, influenza vaccine is safe and well tolerated in IBD patients<sup>[91]</sup>.

## CONCLUSION

It is crucial that physicians involved in IBD care perform a careful investigation for infectious disease before starting immunomodulation. The development of new biological drugs and the increase in their use now and in the future involves a thorough selection of patients with IBD before starting therapy. A careful screening allows the doctor to avoid having to suspend a biological therapy due to the appearance of infections with the risk of reactivation of the underlying disease (Table 1). Although, it is necessary for the IBD community to obtain data on new biomarkers with predictive value on the development of opportunistic infections, in order to set up the necessary preventive measures and to choose the better therapeutic strategies for those high-risk patients. Particular attention must be paid to specific populations, like children and elderly patients, which might deserve peculiar clinical approaches to obtain the maximum clinical benefit and minimize the risks. Routine vaccination schedules are recommended for most IBD patients, following the standard guidelines applicable to general population. However, live vaccinations are contraindicated in immunocompromised patients (Table 2). Patients who are frequent travelers (both for job or recreation) particularly to geographic regions affected with endemic infections also warrant a specific consideration by the IBD specialist. A helpful aid for the clinician is the use of a specific checklist for infectious disease screening and vaccination<sup>[1]</sup>. A strict cooperation with infectious disease specialists is advisable for the correct prevention of opportunistic infections in IBD patients treated with biological therapies.

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