

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

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**Author contributions:** Andrisani G and Guidi L contributed to literature search and wrote the manuscript; Armuzzi A and Marzo M contributed to literature review and proof reading of the manuscript; Felice C, Pugliese D and Papa A performed proof reading of the manuscript.

**Conflict-of-interest statement:** All authors declare no conflict-of-interest related to this paper.

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**Manuscript source:** Invited manuscript

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Received: May 14, 2015

Peer-review started: May 15, 2015

First decision: September 8, 2015

Revised: April 25, 2016

Accepted: June 14, 2016

Article in press: June 16, 2016

Published online: August 6, 2016

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.

Andrisani G, Armuzzi A, Marzo M, Felice C, Pugliese D, Papa A, Guidi L. What is the best way to manage screening for infections and vaccination of inflammatory bowel disease patients? *World J Gastrointest Pharmacol Ther* 2016; 7(3): 387-396 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v7/i3/387.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v7.i3.387>

### 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 |
| Clostridium difficile | Enzyme immunoassay Against toxin A and B and PCR assays  | Not necessary         | Not available  |
| S. Pneumonia          | 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.

## REFERENCES

- Rahier JF, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, Domènech E, Eliakim R, Eser A, Frater J, Gassull M, Giladi M, Kaser A, Lémann M, Moreels T, Moschen A, Pollok R, Reinisch W, Schunter M, Stange EF, Tilg H, Van Assche G, Vigeat N, Vucelic B, Walsh A, Weiss G, Yazdanpanah Y, Zabana Y, Travis SP, Colombel JF. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009; **3**: 47-91 [PMID: 21172250 DOI: 10.1016/j.crohns.2009.02.010]
- Azie N, Neofytos D, Pfäler M, Meier-Kriesche HU, Quan SP, Horn D. The PATH (Prospective Antifungal Therapy) Alliance® registry and invasive fungal infections: update 2012. *Diagn Microbiol Infect Dis* 2012; **73**: 293-300 [PMID: 22789847 DOI: 10.1016/j.diagmicrobio.2012.06.012]
- Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, Langholff W, Londhe A, Sandborn WJ. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol* 2012; **107**: 1409-1422 [PMID: 22890223 DOI: 10.1038/ajg.2012.218]
- Toruner M, Loftus EV, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, Colombel JF, Egan LJ. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008; **134**: 929-936 [PMID: 18294633 DOI: 10.1053/j.gastro.2008.01.012]
- Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, Filippini G, Skoetz N, Francis D, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Lunn MP, Tugwell P, Buchbinder R. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011; **16**: CD008794 [PMID: 21328309 DOI: 10.1002/14651858.CD008794.pub2]
- WHO. Global Tuberculosis report 2015. Available from: URL: [http://www.who.int/tb/publications/global\\_report/en/](http://www.who.int/tb/publications/global_report/en/)
- Afif W, Loftus EV. Safety profile of IBD therapeutics: infectious risks. *Med Clin North Am* 2010; **94**: 115-133 [PMID: 19944801 DOI: 10.1016/j.mcna.2009.08.016]
- Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003; **48**: 2122-2127 [PMID: 12905464 DOI: 10.1002/art.11137]
- Qumseya BJ, Ananthakrishnan AN, Skaros S, Bonner M, Issa M, Zadornova Y, Naik A, Perera L, Binion DG. QuantiFERON TB gold testing for tuberculosis screening in an inflammatory bowel disease cohort in the United States. *Inflamm Bowel Dis* 2011; **17**: 77-83 [PMID: 20848501 DOI: 10.1002/ibd.21329]
- Raval A, Akhavan-Toyserkani G, Brinker A, Avigan M. Brief communication: characteristics of spontaneous cases of tuberculosis associated with infliximab. *Ann Intern Med* 2007; **147**: 699-702 [PMID: 18025446 DOI: 10.7326/0003-4819-147-10-200711200-00066]
- Vaughn BP, Doherty GA, Gautam S, Moss AC, Cheifetz AS. Screening for tuberculosis and hepatitis B prior to the initiation of anti-tumor necrosis therapy. *Inflamm Bowel Dis* 2012; **18**: 1057-1063 [PMID: 21953829 DOI: 10.1002/ibd.21824]
- Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006; **130**: 940-987 [PMID: 16530532 DOI: 10.1053/j.gastro.2006.01.048]
- Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; **105**: 501-523; quiz 524 [PMID: 20068560 DOI: 10.1038/ajg.2009.727]
- Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, Cottone M, de Ridder L, Doherty G, Ehehalt R, Esteve M, Katsanos K, Lees CW, Macmahon E, Moreels T, Reinisch W, Tilg H, Tremblay L, Veereman-Wauters G, Vigeat N, Yazdanpanah Y, Eliakim R, Colombel JF. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014; **8**: 443-468 [PMID: 24613021 DOI: 10.1016/j.crohns.2013.12.013]
- Theis VS, Rhodes JM. Review article: minimizing tuberculosis during anti-tumour necrosis factor-alpha treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2008; **27**: 19-30 [PMID: 17944997 DOI: 10.1111/j.1365-2036.2007.03553.x]
- Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008; **149**: 177-184 [PMID: 18593687 DOI: 10.7326/0003-4819-149-3-200808050-00241]
- Schoepfer AM, Flogerzi B, Fallegger S, Schaffer T, Mueller S, Nicod L, Seibold F. Comparison of interferon-gamma release assay versus tuberculin skin test for tuberculosis screening in inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 2799-2806 [PMID:

- 18684188 DOI: 10.1111/j.1572-0241.2008.02050.x]
- 18 **Andrisani G**, Armuzzi A, Papa A, Marzo M, Felice C, Pugliese D, De Vitis I, Rapaccini GL, Guidi L. Comparison of Quantiferon-TB Gold versus tuberculin skin test for tuberculosis screening in inflammatory bowel disease patients. *J Gastrointest Liver Dis* 2013; **22**: 21-25 [PMID: 23539386]
  - 19 **Shahidi N**, Fu YT, Qian H, Bressler B. Performance of interferon-gamma release assays in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2012; **18**: 2034-2042 [PMID: 22294550 DOI: 10.1002/ibd.22901]
  - 20 **Zabana Y**, Domènech E, San Román AL, Beltrán B, Cabriada JL, Saro C, Araméndiz R, Ginard D, Hinojosa J, Gisbert JP, Mañosa M, Cabré E, Gassull MA. Tuberculous chemoprophylaxis requirements and safety in inflammatory bowel disease patients prior to anti-TNF therapy. *Inflamm Bowel Dis* 2008; **14**: 1387-1391 [PMID: 18452206 DOI: 10.1002/ibd.20496]
  - 21 **Sichletidis L**, Settas L, Spyrtos D, Chloros D, Patakas D. Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. *Int J Tuberc Lung Dis* 2006; **10**: 1127-1132 [PMID: 17044206]
  - 22 **Ananthakrishnan AN**, Guzman-Perez R, Gainer V, Cai T, Churchill S, Kohane I, Plenge RM, Murphy S. Predictors of severe outcomes associated with *Clostridium difficile* infection in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2012; **35**: 789-795 [PMID: 22360370 DOI: 10.1111/j.1365-2036.2012.05022.x]
  - 23 **Ananthakrishnan AN**. Detecting and treating *Clostridium difficile* infections in patients with inflammatory bowel disease. *Gastroenterol Clin North Am* 2012; **41**: 339-353 [PMID: 22500522 DOI: 10.1016/j.gtc.2012.01.003]
  - 24 **Cohen SH**, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol* 2010; **31**: 431-455 [PMID: 20307191 DOI: 10.1086/651706]
  - 25 **Sinh P**, Barrett TA, Yun L. *Clostridium difficile* Infection and Inflammatory Bowel Disease: A Review. *Gastroenterol Res Pract* 2011; **2011**: 136064 [PMID: 21915178 DOI: 10.1155/2011/136064]
  - 26 **Crook DW**, Walker AS, Kean Y, Weiss K, Cornely OA, Miller MA, Esposito R, Louie TJ, Stoesser NE, Young BC, Angus BJ, Gorbach SL, Peto TE. Fidaxomicin versus vancomycin for *Clostridium difficile* infection: meta-analysis of pivotal randomized controlled trials. *Clin Infect Dis* 2012; **55** Suppl 2: S93-103 [PMID: 22752871 DOI: 10.1093/cid/cis499]
  - 27 **Louie TJ**, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, Sears P, Shue YK. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011; **364**: 422-431 [PMID: 21288078 DOI: 10.1056/NEJMoa0910812]
  - 28 **van Nood E**, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; **368**: 407-415 [PMID: 23323867 DOI: 10.1056/NEJMoa1205037]
  - 29 **Kelly CR**, Kahn S, Kashyap P, Laine L, Rubin D, Atreja A, Moore T, Wu G. Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook. *Gastroenterology* 2015; **149**: 223-237 [PMID: 25982290 DOI: 10.1053/j.gastro.2015.05.008]
  - 30 **Hamilton MJ**, Weingarten AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. *Am J Gastroenterol* 2012; **107**: 761-767 [PMID: 22290405 DOI: 10.1038/ajg.2011.482]
  - 31 **Farah R**, Lisitsin S, Shay M. Bacterial meningitis associated with infliximab. *Pharm World Sci* 2006; **28**: 123-125 [PMID: 17004022 DOI: 10.1007/s11096-006-9022-x]
  - 32 **Pilishvili T**, Bennett NM. Pneumococcal disease prevention among adults: Strategies for the use of pneumococcal vaccines. *Vaccine* 2015; **33** (S4): D 60-65 [PMID: 26116257 DOI: 10.1016/j.vaccine.2015.05.102]
  - 33 **Centers for Disease Control and Prevention**. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2012; **61**: 816-819 [PMID: 23051612]
  - 34 **Mandell LA**, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM, Musher DM, Niederman MS, Torres A, Whitney CG. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; **44** Suppl 2: S27-S72 [PMID: 17278083 DOI: 10.1086/511159]
  - 35 **Fiorino G**, Peyrin-Biroulet L, Naccarato P, Szabò H, Sociale OR, Vetrano S, Fries W, Montanelli A, Repici A, Malesci A, Danese S. Effects of immunosuppression on immune response to pneumococcal vaccine in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis* 2012; **18**: 1042-1047 [PMID: 21674732 DOI: 10.1002/ibd.21800]
  - 36 **Kapetanovic MC**, Saxne T, Sjöholm A, Truedsson L, Jönsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2006; **45**: 106-111 [PMID: 16287919 DOI: 10.1093/rheumatology/kei193]
  - 37 **Hameed N**, Tunkel AR. Treatment of Drug-resistant Pneumococcal Meningitis. *Curr Infect Dis Rep* 2010; **12**: 274-281 [PMID: 21308542 DOI: 10.1007/s11908-010-0110-7]
  - 38 **Loras C**, Saro C, Gonzalez-Huix F, Mínguez M, Merino O, Gisbert JP, Barrio J, Bernal A, Gutiérrez A, Piqueras M, Calvet X, Andreu M, Abad A, Ginard D, Bujanda L, Panés J, Torres M, Fernández-Bañares F, Viver JM, Esteve M. Prevalence and factors related to hepatitis B and C in inflammatory bowel disease patients in Spain: a nationwide, multicenter study. *Am J Gastroenterol* 2009; **104**: 57-63 [PMID: 19098850 DOI: 10.1038/ajg.2008.4]
  - 39 **Chevaux JB**, Bigard MA, Bensenane M, Oussalah A, Jarlot S, Belle A, Nani A, Bronowicki JP, Peyrin-Biroulet L. Inflammatory bowel disease and hepatitis B and C. *Gastroenterol Clin Biol* 2009; **33**: 1082-1093 [PMID: 19896313]
  - 40 **Tolentino YF**, Fogaca HS, Zaltman C, Ximenes LL, Coelho HS. Hepatitis B virus prevalence and transmission risk factors in inflammatory bowel disease patients at Clementino Fraga Filho university hospital. *World J Gastroenterol* 2008; **14**: 3201-3206 [PMID: 18506926 DOI: 10.3748/wjg.14.3201]
  - 41 **Biancone L**, Pavia M, Del Vecchio Blanco G, D'Inca R, Castiglione F, De Nigris F, Doldo P, Cosco F, Favassori P, Bresci GP, Arrigoni A, Cadau G, Monteleone I, Rispo A, Fries W, Mallardi B, Stumliolo GC, Pallone F. Hepatitis B and C virus infection in Crohn's disease. *Inflamm Bowel Dis* 2001; **7**: 287-294 [PMID: 11720317]
  - 42 **Longo F**, Hebuterne X, Tran A, Staccini P, Hastier P, Schneider S, Benzaken S, Tirtaine C, Rampal P. [Prevalence of hepatitis C in patients with chronic inflammatory bowel disease in the region of Nice and evaluation of risk factors]. *Gastroenterol Clin Biol* 2000; **24**: 77-81 [PMID: 10679588]
  - 43 **Papa A**, Felice C, Marzo M, Andrisani G, Armuzzi A, Covino M, Mucci G, Pugliese D, De Vitis I, Gasbarrini A, Rapaccini GL, Guidi L. Prevalence and natural history of hepatitis B and C infections in a large population of IBD patients treated with anti-tumor necrosis factor- $\alpha$  agents. *J Crohns Colitis* 2013; **7**: 113-119 [PMID: 22464811 DOI: 10.1016/j.crohns.2012.03.001]
  - 44 **Herbein G**, O'Brien WA. Tumor necrosis factor (TNF)- $\alpha$  and TNF receptors in viral pathogenesis. *Proc Soc Exp Biol Med* 2000; **223**: 241-257 [PMID: 10719836]
  - 45 **Cottone M**, Kohn A, Daperno M, Armuzzi A, Guidi L, D'Inca R, Bossa F, Angelucci E, Biancone L, Gionchetti P, Ardizzone S, Papi C, Fries W, Danese S, Riegler G, Cappello M, Castiglione F, Annese V, Orlando A. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011; **9**: 30-35 [PMID: 20951835 DOI: 10.1016/j.cgh.2010.09.026]
  - 46 **Gisbert JP**, Chaparro M, Esteve M. Review article: prevention

- and management of hepatitis B and C infection in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **33**: 619-633 [PMID: 21416659 DOI: 10.1111/j.1365-2036.2010.04570.x]
- 47 **Gandhi RT**, Wurcel A, Lee H, McGovern B, Boczanowski M, Gerwin R, Corcoran CP, Szczepiorkowski Z, Toner S, Cohen DE, Sax PE, Ukomadu C. Isolated antibody to hepatitis B core antigen in human immunodeficiency virus type-1-infected individuals. *Clin Infect Dis* 2003; **36**: 1602-1605 [PMID: 12802762]
  - 48 **Madonia S**, Orlando A, Scimeca D, Olivo M, Rossi F, Cottone M. Occult hepatitis B and infliximab-induced HBV reactivation. *Inflamm Bowel Dis* 2007; **13**: 508-509 [PMID: 17206687 DOI: 10.1002/ibd.20035]
  - 49 **Loras C**, Gisbert JP, Mínguez M, Merino O, Bujanda L, Saro C, Domenech E, Barrio J, Andreu M, Ordás I, Vida L, Bastida G, González-Huix F, Piqueras M, Ginard D, Calvet X, Gutiérrez A, Abad A, Torres M, Panés J, Chaparro M, Pascual I, Rodríguez-Carballo M, Fernández-Bañares F, Viver JM, Esteve M. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. *Gut* 2010; **59**: 1340-1346 [PMID: 20577000 DOI: 10.1136/gut.2010.208413]
  - 50 **Lok AS**, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]
  - 51 **Hou JK**, Velayos F, Terrault N, Mahadevan U. Viral hepatitis and inflammatory bowel disease. *Inflamm Bowel Dis* 2010; **16**: 925-932 [PMID: 20480515 DOI: 10.1002/ibd.21284]
  - 52 **Melmed GY**, Ippoliti AF, Papadakis KA, Tran TT, Birt JL, Lee SK, Frenc RW, Targan SR, Vasiliauskas EA. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. *Am J Gastroenterol* 2006; **101**: 1834-1840 [PMID: 16817843 DOI: 10.1111/j.1572-0241.2006.00646.x]
  - 53 **Chevaux JB**, Nani A, Oussalah A, Venard V, Bensenane M, Belle A, Gueant JL, Bigard MA, Bronowicki JP, Peyrin-Biroulet L. Prevalence of hepatitis B and C and risk factors for nonvaccination in inflammatory bowel disease patients in Northeast France. *Inflamm Bowel Dis* 2010; **16**: 916-924 [PMID: 19885908 DOI: 10.1002/ibd.21147]
  - 54 **Huang ML**, Xu XT, Shen J, Qiao YQ, Dai ZH, Ran ZH. Prevalence and factors related to hepatitis B and C infection in inflammatory bowel disease patients in China: a retrospective study. *J Crohns Colitis* 2014; **8**: 282-287 [PMID: 24067604 DOI: 10.1016/j.crohns.2013.08.017]
  - 55 **Nardone A**, Anastassopoulou CG, Theeten H, Kriz B, Davidkin I, Thierfelder W, O'Flanagan D, Bruzzzone B, Mossong J, Boot HJ, Butur D, Slaciková M, Panait ML, Hellenbrand W, DE Melker H, Sobotová Z, Icardi G, Andrews N, Pebody RG, VAN Damme P, Kafatos G, Miller E, Hatzakis A. A comparison of hepatitis B seroepidemiology in ten European countries. *Epidemiol Infect* 2009; **137**: 961-969 [PMID: 19102797 DOI: 10.1017/S0950268808001672]
  - 56 **Brunasso AM**, Puntoni M, Gulia A, Massone C. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. *Rheumatology (Oxford)* 2011; **50**: 1700-1711 [PMID: 21690185 DOI: 10.1093/rheumatology/ker190]
  - 57 **Vauloup C**, Krzysiek R, Greangeot-Keros L, Wendling D, Goupille P, Brault R, Brousse C, Mariette X, Emilie D. Effects of tumor necrosis factor antagonist treatment on hepatitis C-related immunological abnormalities. *Eur Cytokine Netw* 2006; **17**: 290-293 [PMID: 17353164]
  - 58 **Viganò M**, Degasperis E, Aghemo A, Lampertico P, Colombo M. Anti-TNF drugs in patients with hepatitis B or C virus infection: safety and clinical management. *Expert Opin Biol Ther* 2012; **12**: 193-207 [PMID: 22188392 DOI: 10.1517/14712598.2012.646986]
  - 59 **Matsuoka K**, Iwao Y, Mori T, Sakuraba A, Yajima T, Hisamatsu T, Okamoto S, Morohoshi Y, Izumiya M, Ichikawa H, Sato T, Inoue N, Ogata H, Hibi T. Cytomegalovirus is frequently reactivated and disappears without antiviral agents in ulcerative colitis patients. *Am J Gastroenterol* 2007; **102**: 331-337 [PMID: 17156136 DOI: 10.1111/j.1572-0241.2006.00989.x]
  - 60 **Doménech E**, Vega R, Ojanguren I, Hernández A, Garcia-Planella E, Bernal I, Rosinach M, Boix J, Cabré E, Gassull MA. Cytomegalovirus infection in ulcerative colitis: a prospective, comparative study on prevalence and diagnostic strategy. *Inflamm Bowel Dis* 2008; **14**: 1373-1379 [PMID: 18452205 DOI: 10.1002/ibd.20498]
  - 61 **Kambham N**, Vij R, Cartwright CA, Longacre T. Cytomegalovirus infection in steroid-refractory ulcerative colitis: a case-control study. *Am J Surg Pathol* 2004; **28**: 365-373 [PMID: 15104299 DOI: 10.1097/00000478-200403000-00009]
  - 62 **Kennedy PG**. Varicella-zoster virus latency in human ganglia. *Rev Med Virol* 2002; **12**: 327-334 [PMID: 12211045 DOI: 10.1002/rmv.362]
  - 63 **Ansari F**, Baker RD, Patel R, Baker SS. Varicella immunity in inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2011; **53**: 386-388 [PMID: 21505365 DOI: 10.1097/mpg.0b013e31821e1917]
  - 64 **Winthrop KL**, Baddley JW, Chen L, Liu L, Grijalva CG, Delzell E, Beukelman T, Patkar NM, Xie F, Saag KG, Herrinton LJ, Solomon DH, Lewis JD, Curtis JR. Association between the initiation of anti-tumor necrosis factor therapy and the risk of herpes zoster. *JAMA* 2013; **309**: 887-895 [PMID: 23462785 DOI: 10.1001/jama.2013.1099]
  - 65 **Sands BE**, Cuffari C, Katz J, Kugathasan S, Onken J, Vitek C, Orenstein W. Guidelines for immunizations in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10**: 677-692 [PMID: 15472534 DOI: 10.1097/00054725-200409000-00028]
  - 66 **Marin M**, Güris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2007; **56**: 1-40 [PMID: 17585291]
  - 67 **Lu Y**, Bousvaros A. Varicella vaccination in children with inflammatory bowel disease receiving immunosuppressive therapy. *J Pediatr Gastroenterol Nutr* 2010; **50**: 562-565 [PMID: 20639716 DOI: 10.1097/MPG.0b013e3181bab351]
  - 68 **Harpaz R**, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2008; **57**: 1-30; quiz CE2-4 [PMID: 18528318]
  - 69 **Kroger AT**, Atkinson WL, Marcuse EK, Pickering LK. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006; **55**: 1-48 [PMID: 17136024]
  - 70 **Zhang J**, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, Saag KG, Baddley JW, Curtis JR. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA* 2012; **308**: 43-49 [PMID: 22760290 DOI: 10.1001/jama.2012.7304]
  - 71 **Cepeda EJ**, Williams FM, Ishimori ML, Weisman MH, Reveille JD. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. *Ann Rheum Dis* 2008; **67**: 710-712 [PMID: 18079191 DOI: 10.1136/ard.2007.081513]
  - 72 **Roset Bahmanyar E**, Paaavonen J, Naud P, Salmerón J, Chow SN, Apter D, Kitchener H, Castellsagué X, Teixeira JC, Skinner SR, Jaisamram U, Limson GA, Garland SM, Szarewski A, Romanowski B, Aoki F, Schwarz TF, Poppe WA, De Carvalho NS, Harper DM, Bosch FX, Raillard A, Descamps D, Struyf F, Lehtinen M, Dubin G. Prevalence and risk factors for cervical HPV infection and abnormalities in young adult women at enrolment in the multinational PATRICIA trial. *Gynecol Oncol* 2012; **127**: 440-450 [PMID: 22940493 DOI: 10.1016/j.ygyno.2012.08.033]
  - 73 **Walboomers JM**, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Muñoz N. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; **189**: 12-19 [PMID: 10451482 DOI: 10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F]
  - 74 **Committee on Practice Bulletins-Gynecology**. ACOG Practice Bulletin Number 131: Screening for cervical cancer. *Obstet Gynecol* 2012; **120**: 1222-1238 [PMID: 23090560 DOI: 10.1097/

- AOG.0b013e318277c92a]
- 75 **Kane S**, Khatibi B, Reddy D. Higher incidence of abnormal Pap smears in women with inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 631-636 [PMID: 17941962 DOI: 10.1111/j.1572-0241.2007.01582.x]
  - 76 **Bhatia J**, Bratcher J, Korelitz B, Vakher K, Mannor S, Shevchuk M, Panagopoulos G, Ofer A, Tamas E, Kotsali P, Vele O. Abnormalities of uterine cervix in women with inflammatory bowel disease. *World J Gastroenterol* 2006; **12**: 6167-6171 [PMID: 17036389]
  - 77 **Seksik P**, Cosnes J, Sokol H, Nion-Larmurier I, Gendre JP, Beaugerie L. Incidence of benign upper respiratory tract infections, HSV and HPV cutaneous infections in inflammatory bowel disease patients treated with azathioprine. *Aliment Pharmacol Ther* 2009; **29**: 1106-1113 [PMID: 19222411 DOI: 10.1111/j.1365-2036.2009.03973.x]
  - 78 **Schunter MO**, Walles T, Fritz P, Meyding-Lamadé U, Thon KP, Fellermann K, Stange EF, Lamadé W. Herpes simplex virus colitis complicating ulcerative colitis: A case report and brief review on superinfections. *J Crohns Colitis* 2007; **1**: 41-46 [PMID: 21172183 DOI: 10.1016/j.crohns.2007.06.004]
  - 79 **François-Dufresne A**, Garbino J, Ricou B, Wunderli W. ARDS caused by herpes simplex virus pneumonia in a patient with Crohn's disease: a case report. *Intensive Care Med* 1997; **23**: 345-347 [PMID: 9083240 DOI: 10.1007/s001340050339]
  - 80 **Ali T**, Yun L, Shapiro D, Madhoun MF, Bronze M. Viral infections in patients with inflammatory bowel disease on immunosuppressants. *Am J Med Sci* 2012; **343**: 227-232 [PMID: 22357111 DOI: 10.1097/MAJ.0b013e31821ff728]
  - 81 **Weinstock DM**. Epstein-Barr virus, lymphoma risk and the potential role of HIV infection in IBD patients undergoing immunosuppression. *Dig Dis* 2010; **28**: 519-524 [PMID: 20926881 DOI: 10.1159/000320411]
  - 82 **Larvol L**, Soule JC, Le Tourneau A. Reversible lymphoma in the setting of azathioprine therapy for Crohn's disease. *N Engl J Med* 1994; **331**: 883-884 [PMID: 8078549 DOI: 10.1056/NEJM199409293311321]
  - 83 **Losco A**, Gianelli U, Cassani B, Baldini L, Conte D, Basilisco G. Epstein-Barr virus-associated lymphoma in Crohn's disease. *Inflamm Bowel Dis* 2004; **10**: 425-429 [PMID: 15475752 DOI: 10.1097/00054725-200407000-00015]
  - 84 **Beaugerie L**, Brousse N, Bouvier AM, Colombel JF, Lémann M, Cosnes J, Hébuterne X, Cortot A, Bouhnik Y, Gendre JP, Simon T, Maynadié M, Hermine O, Faivre J, Carrat F. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009; **374**: 1617-1625 [PMID: 19837455 DOI: 10.1016/S0140-6736(09)61302-7]
  - 85 **Beaugerie L**. Lymphoma: the bête noire of the long-term use of thiopurines in adult and elderly patients with inflammatory bowel disease. *Gastroenterology* 2013; **145**: 927-930 [PMID: 24070724 DOI: 10.1053/j.gastro.2013.09.035]
  - 86 **Weinstock DM**, Ambrossi GG, Brennan C, Kiehn TE, Jakubowski A. Preemptive diagnosis and treatment of Epstein-Barr virus-associated post transplant lymphoproliferative disorder after hematopoietic stem cell transplant: an approach in development. *Bone Marrow Transplant* 2006; **37**: 539-546 [PMID: 16462755 DOI: 10.1038/sj.bmt.1705289]
  - 87 **Chartrand C**, Leeftang MM, Minion J, Brewer T, Pai M. Accuracy of rapid influenza diagnostic tests: a meta-analysis. *Ann Intern Med* 2012; **156**: 500-511 [PMID: 22371850 DOI: 10.7326/0003-4819-156-7-201204030-00403]
  - 88 **deBruyn JC**, Hilsden R, Fonseca K, Russell ML, Kaplan GG, Vanderkooi O, Wrobel I. Immunogenicity and safety of influenza vaccination in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18**: 25-33 [PMID: 21472826 DOI: 10.1002/ibd.21706]
  - 89 **Fiore AE**, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, Iskander JK, Wortley PM, Shay DK, Bresee JS, Cox NJ. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep* 2010; **59**: 1-62 [PMID: 20689501]
  - 90 **Andrisani G**, Frasca D, Romero M, Armuzzi A, Felice C, Marzo M, Pugliese D, Papa A, Mucci G, De Vitis I, Rapaccini GL, Blomberg BB, Guidi L. Immune response to influenza A/H1N1 vaccine in inflammatory bowel disease patients treated with anti TNF- $\alpha$  agents: effects of combined therapy with immunosuppressants. *J Crohns Colitis* 2013; **7**: 301-307 [PMID: 22673636 DOI: 10.1016/j.crohns.2012.05.011]
  - 91 **Rahier JF**, Papay P, Salleron J, Sebastian S, Marzo M, Peyrin-Biroulet L, Garcia-Sanchez V, Fries W, van Asseldonk DP, Farkas K, de Boer NK, Sipponen T, Ellul P, Louis E, Peake ST, Kopylov U, Maul J, Makhoul B, Fiorino G, Yazdanpanah Y, Chaparro M. H1N1 vaccines in a large observational cohort of patients with inflammatory bowel disease treated with immunomodulators and biological therapy. *Gut* 2011; **60**: 456-462 [PMID: 21270121 DOI: 10.1136/gut.2010.233981]

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