

Preparing Patients With Inflammatory Bowel Diseases For Biological Therapies In Clinical Practice

Júlio Maria Fonseca Chebli, Pedro Duarte Gaburri, Lívia de Almeida Costa, Liliana Andrade Chebli, Tarsila Campanha da Rocha Ribeiro, Nayara Peres Aguiar, Carla Malaguti, Maria Cristina Vasconcellos Furtado

Júlio Maria Fonseca Chebli, Pedro Duarte Gaburri, Lívia de Almeida Costa, Liliana Andrade Chebli, Tarsila Campanha da Rocha Ribeiro, Nayara Peres Aguiar, Carla Malaguti, Maria Cristina Vasconcellos Furtado, Division of Gastroenterology, Inflammatory Bowel Disease Center, Federal University of Juiz de Fora, Minas Gerais, 36036-247, Brazil

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Correspondence to: Julio Maria Fonseca Chebli, MD, PhD, Professor, Division of Gastroenterology, Inflammatory Bowel Disease Center, University Hospital of the Federal University of Juiz de Fora, Rua Maria Jose Leal, 296 – Juiz de Fora - Minas Gerais, ZIP: 36036-247, Brazil.

Email: chebli@globo.com
Telephone: +55-32 3232-4915
Fax: +55-32 21023845

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ABSTRACT

Biological therapy has revolutionized the treatment of inflammatory bowel disease (IBD). Although greatly effective, these biologics put the patients at increased risk for developing infections and paradoxical reactions, infections and some types of cancer as lymphomas, the latter one especially when on combination of biologics and thio-

purines. Suitable patient selection, counseling and education are all important items for successful use of the biologics. A comprehensive history to exclude contraindications to this kind of drugs and an emphatic monitoring on guidelines are meaningful steps before starting therapy. Biologics should only be considered if a current evaluation has assured that the patient has active disease. Likewise, it is relevant to exclude disease activity mimickers. To date, biological agents have demonstrated a favorable safety profile in IBD patients. Nonetheless, it is paramount that in clinical practice, commencement of biological therapy be attentively discussed with the patients, widely explaining the potential benefits and risks of such treatment. Before starting biologics use, the patients need to be screened for latent tuberculosis, hepatitis B and C viruses, and HIV infection. Additionally, clinicians must stay vigilant about the risk of infectious tropical diseases reactivation during biological therapy in patients migrating or travelling from tropical endemic areas. Ideally, vaccination status should be checked and updated upon diagnosis of IBD previously immunosuppressant therapy. Current guidelines recommend to IBD adult patients the same routine immunization schedule as for healthy people, strictly avoiding live vaccines during immunosuppressive therapy. Our aim is to review the best strategy to provide an updated overview of important steps involved in the preparation of with IBD patients for biological therapy.

Key words: Inflammatory bowel diseases; Biologics; Immunosuppression; Screening; Immunizations

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INTRODUCTION

Great changes have been noticed in inflammatory bowel

diseases (IBD) therapy, notably during the last decade with immunomodulators and biologics being used increasingly and earlier during the course of disease, especially in a subset of patients whose need changing of the inexorable and destructive course observed frequently^[1,2]. Indeed, accumulating evidence suggests that in high-risk IBD patients, the use of biological agents as monotherapy or in combination with thiopurines may potentially modify the natural course of the disease by decreasing the need of surgical resection and hospitalization rates, as well as to allow clinical remission without steroids^[1,3]. Nevertheless, the growing use and issues concerning to cost and safety of these therapies, mainly infections complications and cancer risk, have been shown to be relevant.

Although there is dissimilarity on routes and timing of biologics administration, the pretreatment assessment protocol is very much alike, regardless of biologic agent used^[4]. For a variety of other immunomodulators (e.g., thiopurines and methotrexate), similar considerations are also applied, and the standard discussed and proposed in this paper can be extrapolated for treatment with these medications. This review aims to provide an updated overview of important steps involved in the preparation of patient with IBD for biological therapy (Table 1), a critical matter looking for meeting the best practice measure on IBD patient’s management in order to improve the ideal outcomes.

RECOGNIZING THE SUITABLE PATIENT FOR BIOLOGICAL THERAPY WHICH IBD PATIENT DESERVES BEING CONSIDERED FOR BIOLOGICS TREATMENT?

The decision-making process to beginning biologics on IBD patients is ground on several features, mainly activity and severity of disease, individual risk evaluation, co-morbidities and appraisal of direct and indirect health care costs.

Both the time-honored approach and according to drug labeling, biological therapy is reserved for patients who have failed, in sequence, to corticosteroids and antimetabolites. Despite of this traditional therapeutic strategy no significant change has been observed in the natural course of IBD^[5]. Nonetheless, a growing deal of evidence corroborates the concept of top-down treatment

or an accelerated step-up approach, rather than the classic step-up approach, at least in Crohn’s disease (CD). Starting a more intensive treatment early in the course of CD could result in better outcomes^[6]. Hence, a proactive and personalized IBD treatment based on activity, severity and risk evaluation have been increasingly adopted in clinical practice. Thus, IBD patients classified as having a low risk condition may be managed with conventional non-biological therapy, while those who are in high risk of severe evolution should to be treated earlier with immunomodulators and/or biologics agents (Table 2), including tumor necrosis factor alpha (TNF- α) inhibitors (adalimumab, certolizumab pegol, golimumab, and infliximab), anti-integrin (vedolizumab) or anti-IL 12/23 (ustekinumab) agents^[7].

CONFIRMATION OF DISEASE ACTIVITY

A backbone for those who treat IBD patients is do not start biologics therapy without a previous accurate evaluation of disease activity to provide suitable treatment. This evaluation must not be based only on present symptoms^[8]. For instance, the Crohn’s Disease Activity Index, which is widely used in clinical trials, has been shown inaccurate for discriminating patients with symptoms due to active CD from patients with irritable bowel syndrome (IBS)^[9]. Also, patients who present abdominal pain, nausea, vomiting, and even diarrhea may have fibrostenotic strictures and are not appropriate for biological therapy^[10]. Accordingly, depending on clinical setting, IBD-related inflammatory activity should be established by ileocolonoscopy, computed tomography (TC) or magnetic resonance (MR) enterography, and/or noninvasive markers, such as fecal calprotectin (FC) levels (higher than 250 μ g/g) or serum C-reactive protein (CRP) levels (higher than 5 mg/L). Ileocolonoscopy remains as the standard gold procedure for assessment of IBD activity, while cross-sectional imaging with enterography is considered sensitive and specific for evaluating mainly small bowel CD. Fecal markers, such as calprotectin concentration has shown significant correlation with endoscopic scores for IBD activity evaluation^[11,12]. It must be pointed that a limitation of CRP is that nearly 15% of patients will not generate CRP in response to infection or inflammation^[13].

EXCLUDING DISEASE ACTIVITY MIMICKERS

Prior to initiating biological therapy for IBD patients, other condi-

Table 1 Check list of important steps for preparing the patient with inflammatory bowel disease for biological and/or immunosuppressive therapy*.

Recognizing the suitable patient for biological therapy	Which IBD patients is a candidate for treatment with biologics?
	Confirmation of disease activity
	Excluding disease IBD mimickers
	Careful watch for contraindications to biologic therapy
Biologic pre-therapy advising	Discussion of costs and pros and cons of biological therapy
	Patient’s information handbill
Screening for latent infections	Tuberculosis (Mantoux [PPD or TST]) skin testing, chest radiographs, or interferon gamma release assays), hepatitis B (HBsAg, IgG anti-HBc, and anti-HBs quantified), hepatitis C (anti-HCV antibody), HIV (HIV-1 and HIV-2 antibodies)
Baseline laboratorial work-up	Complete blood count, urea, creatinine, liver transaminases, C-reactive protein, and fecal calprotectin
	Checking titers for measles (anti-measles IgG) In the absence of measles vaccination or previous infection, hepatitis A virus (anti-HAV IgG), documentation of immunity to varicella zoster virus (i.e., healthcare providers diagnosis of varicella or zoster herpes, documentation of vaccination, or serologic evidence of immunity i.e. anti-VVZ IgG, and screening for Epstein-Barr virus (viral capsid antigen [VCA]-IgG, and Epstein Barr nuclear antigen [EBNA]-IgG)
Assessment and up-to-date immunization records	
Care in health maintenance during follow up	Sun protection, periodic full-body skin surveillance, annual cervical cancer screening for women, remain attentive to signs of adverse drug reactions to biologics

*See text for additional information; †IBD: inflammatory bowel disease; HIV: Human Immunodeficiency Virus; PPD: purified protein derivative; TST: tuberculin skin test.

tions with overlapping clinical presentations need to be excluded. It is worthwhile highlight that IBD patients who are apparently in remission, as suggested by normal inflammatory biomarkers, endoscopic findings and MR or TC enterography, may still have symptoms of abdominal pain, bloating, diarrhea and/or constipation. A significant proportion of these individuals actually have an irritable bowel syndrome-like condition^[14]. In fact, a meta-analysis of patients with IBD demonstrated that 25–46% of those in clinical remission have symptoms consistent with IBS^[15]. Moreover, IBD patients who are in remission, but experience important functional symptoms may mimics active disease, and so receive inappropriate and potentially harmful immunosuppressive therapy. It is also pertinent to point out that in opposition to the minimal investigation approach to the diagnosis of IBS, this condition should only be contemplated in IBD subjects if there is minimal or no evidence of active IBD^[16]. Hence, depending

upon the location and nature of IBD extension, levels of biomarkers of inflammation such as CRP and FC should be measured as well as endoscopic evaluation and/or scanning techniques such as MR or CT enterography should be performed to support the relevance of symptoms and the correct diagnosis^[17].

Bacterial gastroenteritis can simulate activity in IBD, and upon suspicion of acute gastroenteritis, the patient’s faeces should be cultured for pathogenic enteric bacteria^[18]. The incidence of symptomatic *Clostridium difficile* infection (CDI) is higher in IBD population and has increased dramatically in the last decade, regardless immunosuppressive drugs use, hospitalizations, or recent antibiotic exposure^[19,20]. Thus, screening should be done on diarrheal stool in setting of colonic flares and should include nucleic acid amplification assays for *C. difficile* toxins A and B, especially polymerase chain reaction (PCR)^[19]. Enzyme immunoassays sensitivity and specificity for toxin A and B presence in stool are inferior to those of the PCR. However, the screening test with an enzyme immunoassay for the presence of *C. difficile* glutamate dehydrogenase followed by subsequent confirmatory testing with toxin A and B enzyme immunoassays remains useful. Exclusion of cytomegalovirus superinfection is strongly recommended for both patients with colonic IBD presenting steroid-refractory moderate to severe colitis or those who recently used immunosuppressant (especially thiopurines). In this setting colonoscopy with biopsies of ulcerated lesions should be performed to obtain tissue for haematoxylin and eosin staining with immunohistochemistry or Cytomegalovirus (CMV)DNA real-time polymerase chain reaction testing^[21].

Other disorders that can simulate disease activity in IBD and that should be rule out encompass IBD complication (e.g., subocclusive symptoms due to intestinal strictures or presence of an abscess in CD, fistulas, or toxic megacolon, bile salt diarrhea (chiefly in patients with ileocecal resection), small bowel bacterial overgrowth, nonsteroidal anti-inflammatory drugs use, short bowel syndrome, others superimposed conditions such as diverticulitis, segmental colitis associated with diverticulosis, ischemic colitis, celiac disease, carbohydrate malabsorption, depressive disorder, or colon cancer^[22].

Table 2 Risk assessment in inflammatory bowel diseases patients†.

Low risk	Older age
	Non-smokers (for CD)
	Mild to moderate activity
	Localized anatomic extent
	Normal or mildly increased biomarkers
	Normal imaging
	Minimal endoscopic lesions
	Normal perianal examination (for CD)
	Spared rectum (for CD)
High risk	Early age of onset (age < 40 years old or pediatric IBD)
	Need for steroid use to treat the first flare
	Moderate to severe activity
	Extensive disease
	Deep colonic ulcers on endoscopy
	Significant anemia
	High CRP and ESR
	Fistula, abscess or complex perianal fistulas (for CD)
	Severe rectal disease (for CD)
	History of hospitalization or surgery for IBD
Previous <i>Clostridium difficile</i> infection	

*CD: Crohn’s disease; IBD: Inflammatory bowel disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate. †Adapted from references [3,7,20].

Table 3 Summary of contraindications for biologics.

Active, severe infections
Untreated latent tuberculosis
New York Heart Association class II or IV symptoms or left ventricular ejection fraction of ≤ 35%*
History of an acute severe infusion or injection reaction to biologic agent
Multiple sclerosis or another neurological demyelinating disease*
Optic neuritis*
Previous lymphoma*
Current malignancy
Decompensated liver disease
Untreated chronic Hepatitis B virus infection*
Human immunodeficiency virus infection in patients with uncontrolled HIV replication*
History of melanoma, nonmelanoma skin cancer, or recurrent cervical dysplasia†

*Absolute contraindications to anti-TNF-α antagonism; †Relative contraindications to anti-TNF- α antagonism; ♦ Adapted from references [8,23,24]

KEEP A CAREFUL WATCH FOR CONTRAINDICATIONS TO BIOLOGIC THERAPY

Firstly, a meticulous history should be gathered to appraise for possible contraindications to biologic therapies (Table 3). These include active, severe infection, untreated latent tuberculosis, current malignancy or history of lymphoma, a known hypersensitivity to biologic, severe congenital or acquired immunodeficiency, and moderate-to-severe heart failure or a history of demyelinating disorders (for anti-TNF therapy)^[23]. Moreover, anti-TNF-α agents should be used with prudence in patients with mild heart failure as well as in those with a previous malignancy^[24].

BIOLOGIC PRE-THERAPY PATIENTS’ COUNSELING

Once a decision has been taken about the suitability of biological therapy for an individual patient, it is very important to discuss all the circumstances related to this kind of treatment with the patient putting in perspective benefits, cost and risks. Patient education must include a face-to-face discussion or the recommendation of educational materials, including offering a patient’s information leaflet about the

drug^[10]. One of the best ways of obtaining valid information is from a professional organization such as CCFA and/or ECCO. When clinically indicated, the benefits of biologics usually offset the risks, but this should be assessed and discussed on an individual basis with each patient^[25]. An in-depth explanation of the risks of this therapy, including unusual but serious adverse effects such as opportunistic infections and lymphomas (particularly when on combination with thiopurines), must be summarized to patients before beginning therapy^[8]. Patients should be advised that the long-term treatment with thiopurines (mostly >2 years) on monotherapy or in combination with anti-TNF- α agents has been associated with a slightly increased risk of lymphoma, nonmelanoma skin cancer, urinary tract cancer and, likely, uterine cervix abnormalities^[26]. Furthermore, recent data suggest that the risk of melanoma is mildly increased in patients exposed to anti-TNF therapy. Conversely, new biological therapies for IBD (e.g., vedolizumab and ustekinumab) do not appear to be associated with a significantly increased cancer or serious infection risk^[27]. It is foremost pinpoint that these risks are quite low, particularly if screening and prophylactic measures are used. Likewise, these risks must be placed in perspective with the potential for IBD complications or progression in case of not using this kind of treatment, especially biological therapy^[28]. A depicted approach suggested for decreasing the risk of immunosuppression-related lymphomas and other cancers in IBD patients undergoing immunosuppressive therapy is shown in Table 4.

Contact with TB-diagnosed patients during their contagious phase and activities such as revolving the ground in mycosis-endemic areas should be avoided. Moreover, to prevent the occurrence of *Listeria* sp. and *Salmonella* sp. infections, patients should not consume raw eggs, unpasteurized milk products, hot dogs, delicatessen meats (unless reheated at high temperatures), and uncooked meat/fish^[29]. People not immune to varicella (i.e., have not been vaccinated and never had the disease) should avoid contact with varicella patients.

They also should be instructed that biologics use should be stopped and to seek medical care if any of the following symptoms appear during treatment: fever, excessive sweating, weight loss, persistent cough, skin rash, neurologic or articular signals or other unexplained symptoms^[10]. Moreover, patients should know that current smoking has a negative effect on the course of CD, increasing the incidence of flares, the need for steroids, immunosuppressants, re-operations, and get worse response to anti-TNF- α agents^[30]. Hence, patients should be discouraged from smoking, in consequence of the negative effect on the course, treatment and outcome of CD. It is essential a discussion about maintaining biological therapy, because intermittent therapy may predispose to formation of anti-drug antibodies and increased loss of response to anti-TNF agent and/or relapse of IBD^[8]. Also for a patient who is about starting or already on biological therapy and

who has plans to travel to tropical areas (where infectious risks, such as yellow fever and malaria are a concern) it is necessary to perform a travel-related counseling at least one month before travelling, preferentially at a travel medicine clinic^[31].

Therefore, the clear communication between patients and their doctors must include a discussion on the therapeutic benefits of biological therapy. In particular, should be emphasized the potential for improving outcomes i.e. control of inflammation, remission induction, prevention of relapse, steroid-sparing effect, improvement in quality of life, and reducing hospitalizations, surgeries, bowel damage and disability^[32,33]. Eventually, proper education is critical, and the correct understanding of the risks and benefits of biologics by patients depends chiefly on what and how information is transmitted by the doctor^[28].

SCREENING FOR LATENT INFECTIONS

The use of biological agents in the treatment of autoimmune diseases, including IBD has been widely associated with an increased risk of reactivation of various latent infections. International guidelines recommend screening for infectious disorders before initiating these agents^[29,31]. In particular, we will approach the screening for latent tuberculosis (LTB) infection, viral hepatitis, and human immunodeficiency virus (HIV). Patients migrating or travelling from tropical endemic areas of the world, including South America, Africa and Asia, may be at greater risk from a myriad of bacterial or parasitic infection, such as *Strongyloides stercoralis*, *Leishmania* spp, *Trypanosoma cruzi*, *Mycobacterium leprae*, among others, and so clinicians must stay vigilant about the risk of reactivation of infectious tropical diseases in migrant or travelling patients who receive immunosuppressant or biological treatment^[34].

TUBERCULOSIS

Treatment with biologic agents, mainly the TNF- α inhibitors, increase the tuberculosis (TB) reactivation risk in 2 to 8 fold when compared to the general population, and of the poorer outcomes if active TB develops^[35]. The relative risk is higher with infliximab (18.6%) and adalimumab (29.3%) than others biologic agents^[35,36] and greater when these drugs are combined with another immunosuppressive agents than in monotherapy^[35].

Screening and treatment of active or latent TB infection (LTBI) are fundamental and should be done in all patients considering the use of anti-TNF- α therapy^[37,38], reducing by up to 85% the risk of TB reactivation^[37]. In spite of these strict care, TB active still occur in 1-2% of these patients^[35,37], whose occur mainly 3-4 months after anti-TNF α therapy starting. It might be explained by reactivation of LTBI or failure in diagnosing LTBI previously. When it occurs lately it is in

Table 4 Suggested approach for decreasing the risk of immunosuppression-related lymphomas and cancers in inflammatory bowel diseases patients*.

Work-up for clinically silent pre-existing neoplasm in patients older than 50 years, including screening for breast cancer in women and prostate cancer in men
Use sun protection, including wearing sun-protective clothing, using sunscreen with SPF of 30 or higher, seeking shade limiting activities outdoors between 10 AM e 4 PM, and avoiding indoor tanning
Annual full-body skin surveillance by a dermatologist
Consider not using combination therapy of anti-TNF- α and thiopurines in young male patients (age < 35 years) due to higher risk of hepatosplenic T-cell lymphoma in this clinical setting, unless this is considerate to be the best approach for that specific patient (in this case, limit the duration of the combined treatment to two years)
Avoid using thiopurines on older patients (> 65 years; > risk of lymphoma) and in young male IBD patients who are Epstein-Barr virus-seronegative (> risk of post-mononucleosis lymphoma)
Women on immunosuppressive therapy should undergo annual cervical cancer screening as well as to order human papillomavirus vaccination for IBD patients between 9-26 years old, preferentially before the initiating immunosuppressant

*Adapted from references [26,78].

general, consequence of new infection. Although negative screening does not exclude TB infection, all patients need to be closely monitored for reactivation of TB^[35].

Accurate screenings of LTBI followed by the prophylactic therapy reduce the risk of TB reactivation^[39,40]. There is no gold standard test for the diagnosis of LTBI^[35]. This screening is performed using epidemiological data (contact with patients with tuberculosis, travel to TB endemic areas or prior history of TB treatment); symptoms of suspected TB (cough, fever, hemoptysis, weight loss) or history of vaccination; physical examination; chest radiography (to exclude active TB); Tuberculin Skin Test (TST) and/or more specific *Mycobacterium tuberculosis* interferon gamma release assay (IGRAs) test^[35,39] (Figure 1).

The chest radiography is important to exclude active TB and to provide additional evidence of LTBI because 9% of the positive screened patients were investigated exclusively due to abnormal chest radiography^[37]. TST and IGRAs detect immunological evidence of host sensitization to *Mycobacterium tuberculosis* antigens but both tests are unable to distinguish active and LTBI^[41]. In patients receiving immunosuppressant these tests have a suboptimal performance and are often associated with false-negative results, however, IGRAs are less influenced by these drugs^[35].

TST is performed according to the Mantoux method and an induration ≥ 5 mm or a conversion after an initial negative test is considered to be positive. TST have a low sensitivity and specificity and the results can be distorted by a prior BCG (Bacillus Calmette-Guerin) vaccination, but it is almost insignificant in adults aged > 30 years^[37] and considerably reduced 2 years after vaccination^[1]. In patients who have been taking immunosuppressive drugs for > 3 months or corticosteroids for > 1 month, or yet with significant protein-calorie malnutrition, this test may also shows false-negative results^[37,40].

IGRAs is delivered in commercial kits such T-SPOT and QuantiFERON. Both commercial kits use purified antigen for *Mycobacterium tuberculosis* to stimulate peripheral blood lymphocytes to produce interferon gamma. In patients using immunosuppressive therapy, this test is associated with negative or indeterminate results in some studies^[36], but have higher sensitivity and specificity than TST, and does not exhibit cross-reactivity with BCG vaccine^[35].

In patients with IBD receiving anti-TNF therapy, TB infection may be disseminated, severe and occasionally fatal. By this way, it is necessary to increase the sensitivity for detecting LTBI. The sensitivity of these tests depends on a number of factors, such as the TB incidence in the country, previous vaccination and the use of immunosuppressive drugs^[39]. The United States guidelines recommend replacing the TST by IGRA tests to improve the diagnosis accuracy, however IGRA test is not yet disposable in every country and TST is yet the most frequently employed for being cheaper and more accessible^[39,41]. Others recommend TST first, followed by IGRAs in patients with a high pretest probability of having LTBI (history of contact with case of active TB), previous BCG vaccinations or TST borderline or suspected false-negative^[35,36]. In patients using immunosuppressive drugs the TST and IGRAs may lead to false negative results and some authors recommend using both methods to increase the sensitivity^[42,43]. Either positive test is a valid method to diagnose LTBI^[35].

The diagnosis of LTBI should be considered in patients with a recent or past exposure to active TB, positive initial or booster TST and/or positive IGRA; without evidence of active TB in the chest radiography^[35,37]. If chest radiography suggest previous untreated tuberculosis, patients should be eligible for treatment after exclusions of active tuberculosis, regardless the IGRA or TST test results^[44,45].

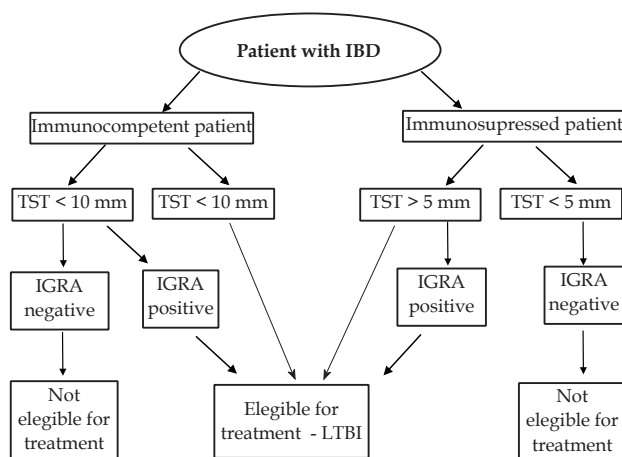


Figure 1 Flow chart for treatment of latent tuberculosis infection in IBD patients. Adapted from references^[4,43]; * IBD - inflammatory bowel disease; TST - tuberculin skin test; IGRA - interferon-gamma release assay; LTBI - latent tuberculosis infection.

If we do not have conditions of performing IGRA test, we can use clinical history and physical examination, associated with chest radiography and TST. A TST of ≥ 5 mm in patients who have HIV, organ transplants, receiving corticosteroids or other immunosuppressive drugs, a recent TB contact or a chest-radiography consistent with prior TB (linear opacities, pleural thickening, calcification > 5 mm or upper lobe fibronodular disease), with no previous anti-TB treatment, should be considered as LTBI. In face to LTBI the treatment is not indicated for those with fibrotic lesions if they had a history of previous treatment for TB, unless it is suspected a newly acquired TB infection^[35]. In cases of uncertainty about whether there is a medical history or radiological suspicion of LTBI, TB prophylaxis must be initiated, and the patient should be referred to a pulmonary specialist. LTBI treatment regimens in patient's candidate for receiving anti-TNF treatment vary among in different countries. The treatment options include daily isoniazid for 6 or 9 months, with protection rates against TB infection between 60-80% and 90%, respectively; or rifampin plus isoniazid for 3 months^[35]. It is not defined how long it is necessary for LTBI treatment before starting anti-TNF- α therapy. The minimum considered time delay is 3-4 weeks. The benefit of earlier anti-TNF- α treatment has to be weight by a risk of TB reactivation^[36]. The simultaneous initiation of LTBI and anti-TNF therapy may be considered in urgent cases^[35].

In summary, in cases that the chest-radiography is normal and TST has < 5 mm of induration, the anti-TNF- α therapy can be started. However, if chest radiography is abnormal, three sputum samples must be examined for TB^[45]. If its result is negative, the treatment with isoniazid for LTBI must be started for six or nine months, delaying biological starting for at least 3-4 weeks. If positive, a complete treatment for active TB must be initiated for 6 to 12 months, deferring anti-TNF- α as long as we can, if possible until the end of TB treatment. If TST has > 5 mm of induration, sputum samples are negative for TB, and chest radiograph is normal, treatment for LTBI should be initiated, but if chest-X-Ray is abnormal, the treatment of active TB must be started, independent of sputum investigation being positive or negative. If the chest-X-Ray shows images consistent with residual TB, the patient should be referred to a pulmonary specialist^[44].

The TB screening cannot fully prevent TB associated with anti-TNF- α ^[37]. Moreover, there are no methods of confirming whether LTBI has been adequately cured after the treatment^[35]. During anti-

TNF- α therapy and at least 6 months after cessation of treatment, all patients should be monitored for signs and symptoms of TB disease^[36]. To repeat the TB screening during the anti-TNF- α therapy seems a rational approach to minimize this issue, although the best procedure remains unknown and there are no routine tests to be done during treatment^[36,37]. Therefore, monitoring is based in clinical symptoms and signs of recurrent TB^[35]. The American College of Rheumatology and CDC recommend annual TB testing only for patients with increased risk for TB infection. These patients should be tested with TST or IGRA if previously tested negative. In patients who had these tests positive at baseline this result remain positive after LTBI treatment and is not helpful to assess the risk of new infection. It is very relevant to repeat tests in patients with ongoing or new TB risk. There are no specific recommendations to screening patients traveling to Tb endemic areas^[36].

TB disease in patients receiving anti-TNF- α therapy is more likely to be extra pulmonary (60%) and disseminated (25%), with poor outcome and mortality rate as high as 17%^[35]. The tests to detect LTBI are not absolutely specific and sensitive to recognize all patients who will develop active TB^[36,37]. This diagnosis should be suspected in patients who lived in close contact with known patients with active TB or in endemic areas, those who experience fever, weight loss, night sweats, even in the absence of pulmonary symptoms. Anti-TB treatment should be started if this diagnosis is strongly suspected. The optimal duration of anti-TB therapy has not been well defined^[35] and to consider prolonged course (i.e., 9 months) may be prudent. The anti-TNF- α therapy should be discontinued temporarily and the time to restart these drugs are unknown^[36]. It is considered safe to delay anti-TNF- α resumption until the anti-TB therapy is finished, but biological therapy can be started after two months if patients require early resumption of anti-TNF- α agent and demonstrate favorable response to anti-TB therapy^[35,44].

HEPATITIS B AND C

Hepatitis B

In consequence of potential risk of hepatitis reactivation during immunosuppression, current management of IBD patients requires screening for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection before starting immunosuppressive treatment^[46]. Hepatitis B is an important disease worldwide since that one-third of the world's population has been infected with HBV^[47]. Prevalence of HBV and HCV infection in IBD has been shown to be similar to that of the general population of reference and lower than that observed in previous studies what was probably related to adoption of preventive measures such as vaccination^[48]. Reactivation of HBV replication with increase in serum HBV DNA and ALT level has been reported in 20% to 50% of hepatitis B carriers undergoing immunosuppressive or cancer chemotherapy^[49]. Considering that IBD patients may need immunosuppressive therapy at any point of disease natural course, including combination of biological agents and thiopurines, and there is an increasing trend towards earlier use of these drugs for longer periods, it is necessary to screen all patients for HBV infection at diagnosis, because reactivation of HBV and hepatic decompensation can occur^[50].

As HBV infection can be prevented by vaccination, those who are HBV markers negative must receive immunization before immunosuppression^[47]. Liver dysfunction in patients with IBD treated with immunosuppressant is more frequent and severe in those with HBV than in HCV carriers and is associated with combined immunosuppression^[51]. Serological assessment for HBV must include hepatitis

B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) titers, and hepatitis B core antibody (HBcAb)^[50]. It is imperative to vaccinate patients who lack serum protector level of anti-HBs (i.e., ≥ 10 U) before anti-TNF therapy, because an increasing number of hepatitis B reactivation has been reported when no preventive measure is adopted. HBV vaccination is recommended in all HBV seronegative patients with IBD^[46,50]. A full vaccination course (0, 1, and 6 months) for HBV is recommended in patients that have not received vaccine previously, and a booster dose must be used in those vaccinated when anti-HBs levels is below 10 units. Higher doses of the immunizing antigen may be necessary to achieve success. Serological response should be measured 1 to 2 months after the completion of vaccination. In non-responders patients a new complete vaccination course should be recommended with anti-HBV vaccination in double-dose accelerated schedule (i.e., 0, 1 and 2 months) before starting immunosuppressive treatment. Young patients vaccinated at the beginning of anti-TNF therapy displayed better response^[46]. Long-lasting effective protection is greatest in patients vaccinated before of starting immunosuppressive agents^[46,50]. Vaccine response was around 46% using double doses in patients with IBD receiving anti-TNF drugs^[52]. If the patient remains non immune, it is important offer booster with a double dose of hepatitis B vaccine or a combined hepatitis A/B vaccination^[53,54], although the response to vaccination/revaccination is lower in patients under anti-TNF therapy. However, AZA seems not to influence vaccine response^[54]. Modified dosing regimens, including doubling the standard antigen dose or administering additional doses, might increase response rates^[52]. Younger patients vaccinated at the beginning of anti-TNF therapy and receiving it as a monotherapy showed better response. Hepatitis B core-related antigen (HBcrAg) is a novel serum marker that correlates with intrahepatic HBV activity and HBcrAg positivity is a significant risk factor of HBV reactivation in HBsAg-negative, anti-HBc positive patients undergoing high-risk immunosuppressive therapy and can potentially have a role in identifying patients who will best benefit from prophylactic nucleoside analogue treatment^[55].

It has been recommended by American Association for the Study of Liver Disease (AASLD)^[56] as well as the European Association for Study of the Liver (EASL)^[57] the early prescription of nucleoside/nucleotide analogues (NAs) for all HBsAg positive patients who need immunosuppressive therapy. This strategy must be adopted at least 7 days before starting thiopurines and biologics agents and continued for 6 months to 1 year after ending therapy, regardless of the number and type of immunosuppressants used, because HBV reactivation may occur even after drugs withdrawal^[56-58]. Recently, the EASL recommended that: a) all candidates for chemotherapy and immunosuppressive therapy should be tested for HBV markers prior to immunosuppression; b) all HBsAg-positive patients should receive any of the following antiviral agents as treatment or prophylaxis: entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide c) HBsAg-negative, anti-HBc positive subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation^[57]. Ideally, immunosuppressive therapy should be delayed, if possible, until a negative HBV DNA viral load was obtained, which may require 2–3 months^[57-59]. Patients suffering from moderate/severe IBD frequently cannot wait for so long period of time. Prophylaxis should be ordered regardless of the number and type of immunosuppressant used, whether steroids, immunomodulators, or biologics^[59]. Tenofovir/entecavir is preferred over lamivudine as nucleos(t)ide analogues due to their better resistance profile. Table 5 summarizes a suggested approach for management of IBD patients that are infected with hepatitis B or C virus and need immunosuppresses or biological therapy.

There is a potential for competitive inhibition for active tubular secretion if lamivudine and methotrexate are co-prescribed, which may result in increased serum concentrations of either or both drugs with associated potential toxicity. This competitive inhibition for renal tubular secretion may also arise with tenofovir disoproxil fumarate and methotrexate. This combination would require close monitoring of renal function^[46]. Although less common, HBV reactivation can also occur during immunosuppressive therapy in patients with occult HBV infection defined by a quiescent infection in HBsAg/anti-HBc-positive or anti-HBc-positive/anti-HBs-positive patients but with persistent DNA in the nucleus of hepatocytes^[60]. The patients with occult HBV should be monitored for alanine aminotransferase and HBV DNA during throughout their treatment with immunosuppressant^[60,61]. If anti-TNF- α therapy is used in HBV-infected patients who also receive concomitant anti-viral treatment, the outcome from case reports has been good for biologic agents, with no evidence of viral reactivation. Serum aminotransaminase level remained normal and there was no increase in viral load during treatment with anti-TNF- α agents^[61]. Furthermore, almost all cases of HBV reactivation associated with infliximab occurred in patients receiving concomitant treatment with other immunosuppressant^[58,61].

Hepatitis C

In HCV patients, concurrent IBD represented in the past a relative contraindication to IFN-based treatment due to the risk of IBD exacerbation although the management of patients with chronic viral hepatitis or IBD has been revolutionized in the last years by the introduction of highly effective treatments^[46]. It was also demonstrated that treatment of IBD with infliximab in HCV patients did not result in flares in hepatic biochemical tests, and there was improvement in the IBD disease activity score^[59]. Moreover, there are no studies directed at the effects of corticosteroids and immunomodulators on the course of HCV, except some case reports^[59,62].

To date, there is no conclusive information on the safety of immunosuppressive drugs in HCV among IBD patients. From a clinical standpoint, the management of these patients is challenging due to many reasons: drugs used in the treatment of IBD may result in liver toxicity, thus leading to worsening of the coexisting liver disease; im-

munosuppressive regimens used to treat IBD may lead to viral reactivation which can progress to liver failure in selected cases; moreover, drug-drug interactions (DDIs) between therapies administered for viral hepatitis or IBD may lead to reduced response rates or unexpected adverse events^[46]. However, it has been observed that anti-TNF- α drugs seem to reduce inflammation through TNF- α inhibition, playing a role in the pathogenesis of HCV^[59]. These patients appear to be at low risk, although long-term safety studies are needed^[63,64]. On the other hand the recent development of direct acting antiviral drugs (DAAs) to cure HCV infection paved the way to safely achieve viral eradication in IBD patients. Indeed, the elimination of interferon from the standard of care treatment has allowed extending eligibility to antiviral therapy also in patients suffering from immune-mediated diseases like IBD^[64,65].

While efficacy of DAAs in registration trials and real-life studies exceeds 95% across nearly all genotypes in the HCV general population, more data are currently needed in special populations like IBD patients, although there is no theoretical reason to suspect a reduced DAAs efficacy in this patient population.

Concerning safety, the only topic to address is the potential DDIs between DAAs and immunosuppressive drugs, especially biologics agents. Although there are limited pharmacokinetic DDIs studies between HCV DAAs and drugs used in the treatment of IBD, the understanding of drug disposition in IBD therapy can lead to predict potential DDIs. Administration of ledipasvir–sofosbuvir has not been studied with prednisone, azathioprine, or methotrexate. However, a clinically significant interaction with prednisolone, azathioprine/6-mercaptopurine, or methotrexate is unlikely based on their metabolic pathways. While co-administration has not been studied, no clinically significant interaction is expected between daclatasvir and azathioprine (6-mercaptopurine) or prednisone considering the pharmacokinetics of both drugs. A potential interaction exists between daclatasvir and methotrexate, resulting in increased concentrations of methotrexate. No overlap in the metabolic pathways of ritonavir-boosted paritaprevir, ombitasvir plus Dasabuvir and azathioprine/6-mercaptopurine have been noticed, and so no drug interactions are expected to occur^[46]. However, methotrexate levels may be increased in the association to grazoprevir–elbasvir, while no DDIs are ex-

Table 5 Strategies for management of IBD patients that are infected with hepatitis B or C virus and need immunosuppresses or biologics therapy*

Hepatitis B Virus (HBV).	
Before treatment of all IBD patients	Screening for hepatitis B: HBsAg, anti-HBc and anti-HBs
	Patients HBsAg +: evaluate HBeAg, Anti-HBe and HBV- DNA
	Patients HBV negative: must be vaccinated and checked for anti-HBs levels 1-2 months after the last dose of vaccine.
	Anti-HBs titer must be rechecked every two years after starting therapy
HBV Active Infection: (HBsAg +, HBeAg + or Anti-HBe +, ALTñ, HBV- DNA +)	Antiviral therapy with third generation NA(s) with high barrier to HBV resistance: ETV, TDF or TAF
	The time of therapy will be guided by liver disease response.
HBV Inactive carrier: (HBsAg +, Anti-HBe +, normal ALT, HBV- DNA < 2.000 UI/ml)	Antiviral prophylaxis employing NA(s) with high barrier to HBV resistance (ETV,TDF or TAF)
	Antiviral therapy should be started 1 - 3 weeks before IST and continue through 6 - 12 months after stopping it.
Occult HBV infection: (HBsAg -, Anti-HBc +, anti-HBs ±)	Monitoring HBsAg and HBV- DNA every 3-4 months
	In case of seroconversion, antiviral therapy have to be started
Hepatitis C virus (HCV)	
Before treatment of all IBD patients	Screening for anti-HCV: if anti -HCV +, evaluate HCV - RNA
	The use of immunomodulators and biologics will be decided according the severity of liver disease; anti-TNF- α therapy are contraindicated on decompensate liver cirrhosis (Child B and C).
During treatment	Laboratory liver tests (ALT, AST, Albumin, Bilirubin and Platelet counts) must be monitored every 3 months

NA(s) - nucleoside/nucleotide analogues; ETV - Entecavir ; TDF - Tenofovir disoproxil fumarate; TAF - tenofovir alafenamide; IST - immunosuppressive therapy. *Adapted from references [46,57,58].

pected with thiopurines or prednisone. Moreover, no interaction is expected between simeprevir and thiopurines or methotrexate, but association with prednisolone may increase its systemic exposure, and although no dose adjustment of prednisone is required, monitoring for steroids side effects is recommended. If steroid use is inevitable for control IBD exacerbations, the lowest beneficial dose and slow tapering is advisable^[58]. A significant potential interaction exists when ribavirin and azathioprine (or 6-mercaptopurine) are associated, since that it can lead to increased levels of 6-methylthioinosine monophosphate which is associated with myelotoxicity^[66].

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

An over-expression of serum TNF has been demonstrated in all stages of HIV infection and theoretically, there may be a favorable effect of anti-TNF therapy in patients with HIV^[67]. An interestingly argument favoring the use of anti-TNF inhibitors in HIV- infected patients is the safety of its use, since no increase in the mortality rate has been recorded^[68]. Furthermore, HIV-1 symptoms may be improved in treated patients, even if anti-TNF therapy could favor the immunosuppressive status of the patients and thus increase the risk of opportunistic infections^[67]. Additionally, anti-TNF agents has been reported to be well-tolerated in patients com HIV, with no enhancement of the rate of opportunistic infections, unless they had ongoing uncontrolled HIV replication^[69,70]. Anti-TNF therapy may be used for the treatment of IBD and others autoimmune diseases in a multidisciplinary approach during therapy, without enhancing the plasma viremia in patients whose HIV disease is under control by combination antiretroviral therapy^[71]. In present, no study has still assessed the safety of new biologics in IBD population.

IMMUNIZATIONS

Patients suffering from IBD need treatment that includes several immunosuppressant and biological agents. It is acknowledgement that immunosuppressed individuals, when exposed to infectious pathogens, can develop routine and opportunistic infections, and on occasion severe and life-threatening infections^[54]. It is also known that there are infections which are vaccine prevented illness, and the management of IBD patients must starts with vaccination and immunization strategies, ever when possible at diagnosis time^[72,73]. The immune system in patients with IBD is dysregulated independent of disease activity. Immune dysregulation occurs both in patients who are immunosuppressant-naive and immunosuppressant-experienced^[74]. Thus, it is important to view all patients with IBD as having an altered immune system^[75]. The quality of the immune system will guide the vaccination effectiveness, with quantitatively normal levels of IgG, IgA, IgM and IgE, maintaining humoral and cellular immunity.

An adequate response after vaccination in patients with CD and ulcerative colitis is expected, even in the absence of immunomodulatory therapy, since that an exaggerated response to various external stimuli happens in IBD patients^[76]. Few strategies have been created to safely guide the management of IBD patients using immunosuppressive therapy^[76,77] and so we need to keep in mind the importance of adopting the vaccination status during the first office visit. It is necessary educating patients as well as gastroenterology team about the vaccination importance of IBD patients in order to increase their vaccination rate, especially before immunosuppressive therapy. Moreover, it is necessary to evaluate occupation, housing and travel to endemic areas, risks of exposure, as well as the updated vac-

ination card, according to general instructions for immunization schedule recommended by the Ministry of Health. It should also be emphasized that vaccination in these patients is not associated with reactivation of IBD^[73,78]. However, in those patients using immunosuppressive therapy, it must be taken a strong care prior to vaccine administration, once that usually no live vaccines can be used, due to the risk of infectious agents spread^[76]. When possible, evaluation of antibodies to some infectious diseases, such as chickenpox, might be performed to assess whether or not specific vaccines are required.

LIVE ATTENUATED VACCINES

One of the most important topic in IBD patients vaccination is to consider if the infectious agent is live and attenuated or inactivated and killed, since that the first one do not contain microorganisms and can be safely used, while the second has weak but live agents that will meet an also weak immunological system. In consequence measles, mumps, rubella, polio (Sabin), yellow fever, varicella, BCG, oral typhoid and inhaled influenza (intranasal) cannot be administered to immunosuppressed patients, including those on current treatment or those that recently (e.g. within last 3 months) received prednisone 20mg/day or equivalent for two weeks or more, azathioprine, 6-mercaptopurine or methotrexate, biologic agents, or with severe malnutrition^[76,78]. In case of being required vaccination for mumps and rubella, it must waited at least 4 to 6 weeks to start treatment with immunosuppressant; in case of patients who need travelling to areas where yellow fever is endemic, immunosuppressive therapy would be started one to three months after vaccination and in other cases at least one month after vaccination should be waited^[72,76].

It is mandatory to assess varicella immune status on occasion of the diagnosis and prior to starting any immunosuppressive therapy in IBD patients. Those who do not have a history of previous varicella, herpes zoster or vaccination for varicella, need to have assessed their serum antibody titers^[54,72]. The ECCO guidelines recommend immunization with varicella-zoster virus (VZV) vaccine at least 3 weeks before starting immunomodulator therapy, and preferably at diagnosis of IBD, if the medical history of chickenpox, shingles or VZV vaccination is negative^[50]. While patients using short-term corticosteroid therapy (≤ 2 weeks), low doses of methotrexate, azathioprine or 6-mercaptopurine have safely received zoster vaccine, most experts recommend strict caution in such cases due to the theoretic risk of illness dissemination^[79]. Although not specific for IBD patients, the recent guideline of the Infectious Diseases Society of America (IDSA)^[77] may be a nice guide. In short, the IDSA guideline recommends that zoster vaccine: (a) Should be given to patients aged ≥ 60 years if it can be administered ≥ 4 weeks before beginning highly immunosuppressive therapy; (b) Should be considered for varicella-positive patients (i.e., persons with a history of varicella or zoster infection or who are varicella zoster virus seropositive with no previous doses of varicella vaccine) aged 50-59 years if it can be administered ≥ 4 weeks before beginning immunosuppressive therapy; (c) Should be administered to patients aged ≥ 60 years who are receiving therapy considered to induce a low level of immunosuppression (i.e., those receiving daily corticosteroid therapy with a dose < 20 mg of prednisone or equivalent for ≥ 14 days or receiving alternate-day corticosteroid therapy; or using methotrexate ≤ 0.4 mg/kg/week, azathioprine ≤ 3.0 mg/kg/day, or 6-mercaptopurine ≤ 1.5 mg/kg/day); (d) Should not be administered to highly immunocompromised patients (i.e., receiving daily corticosteroid therapy with a dose ≥ 20 mg of prednisone or equivalent for ≥ 14 days; or using certain biologic immune modulators, such as a TNF- α blocker or rituximab).

INACTIVATED VACCINES

Inactivated vaccines do not contain live microorganisms and so are well tolerated by immunosuppressed patients. However, there may be a lesser ability to be followed by satisfactory seroconversion and to keep efficient antibody titers at protective levels^[78]. Pneumococcal and influenza (injectable), the two most common infections in adults with high morbid-mortality in patients over 65 years old, can be prevented with vaccination. The vaccines that contain infectious agents dead or inactivated also includes rabies, injectable typhoid, hepatitis A, HPV (Human Papilloma Virus), meningococcal and tetanus and diphtheria for adults^[54,73]. Infection with hepatitis B virus (HBV) can be prevented by vaccination with hepatitis B surface antigen (HBsAg), which induces HBsAg-specific antibodies and T cells, and do not have any harmful effect in immunosuppressed patients^[75].

All individuals with IBD should receive the inactivated vaccine against influenza on an annual basis independently of the patient's immune status^[54]. The intranasal influenza vaccine is contraindicated in immunosuppressed individuals. In addition, at least one dose of pneumococcal vaccine should be administered, with revaccination after 5 years, to patients who are over 65 years and/or immunosuppressed^[75,77]. However, PPSV23 has been demonstrated effective in preventing invasive pneumococcal disease (IPD) in adults but, approximately 20%-25% of IPD cases and 10% of community-acquired pneumonia cases in adults aged ≥ 65 years are caused by serotypes unique to PCV13. Broader protection against pneumococcal disease is expected through use of both PCV13 and PPSV23 in series^[80].

Tetanus and diphtheria vaccines should be administered every 10 years and, at least once in a lifetime, it should be associated with pertussis. The meningococcal vaccine may be given to IBD patients, especially those at greater risk for this infection, like the ones submitted to splenectomy^[75,81]. The hepatitis B vaccine response can be decreased during immunosuppressant use and when anti-HBsAg

titers are undetectable or lower than 10 mU/mL, a new schedule with the double of each of the three doses (40 μ g) or a booster dose at 12th month must be applied. If there is urgency to start immunosuppressive therapy, shortening the vaccine scheme is allowed, with every dose at 0, 1 and 2 months of interval, instead of conventional scheme of 0, 1, and 6 months^[75-77,81]. In cases of hepatitis A, if no circulating antibodies are observed, the indication is 2 doses and a booster after 10 years^[75,81].

HPV vaccine is recommended to both gender between 9-26 years old before or newly initiated into sexual activity, as well as to patients with a history of condyloma, HPV infection (positive DNA test) or with abnormal Pap smears^[54,75]. Women with IBD with or without the use of immunosuppressant, regardless of sexual activity, should also be vaccinated because they are considered at high-risk. General vaccination strategies are listed in the Table 6.

VACCINATION OF NEWBORNS

Women with IBD who used biologics agents while pregnant, especially during the last trimester of pregnancy should have their newborns approached for vaccination. Since that the presence of circulating drug in newborns up to six months postpartum has been reported live virus vaccines as those for rotavirus and BCG should not be administered^[82,83]. The same rationale should be applied to all biologics used in IBD therapy although there have been no studies about this matter to date. All vaccines with dead or inactivated viruses can be safely administered^[83,84].

It must be highlight that monoclonal antibodies can cross the placenta from the second trimester, although they seem to be safe, at least in the short term^[82,85]. However, live vaccines should be avoided in children with in uterus exposure to biologics for at least the first 6 months of life. Therefore, it has been proposed that anti-TNF therapy should be withdrawal during the second trimester in stable IBD pa-

Table 6 Strategies and check list for IBD patient's vaccination*.

Topics to be checked at IBD diagnosis or on first clinical visit	- Vaccination card
	- Serologic antibodies levels
	Measles, Rubella and Mumps: when history of past vaccination is unknown.
	Varicella: if previous infection and past vaccination are unknown.
	Hepatitis A: unless there are protecting anti-HAV IgG antibodies in the 5 year after vaccination. Hepatitis B: unless there are protecting anti-HBs titles in the 5 years after vaccination.
Inactivated vaccines that should be offered to specific IBD patients, regardless of degree of Immunosuppression	Influenza (injectable only): yearly.
	Pneumococcus: 13-Valent Pneumococcal Conjugate Vaccine (PCV 13) followed by 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV 23)**.
	Tetanus and diphtheria: every 10 years; one dose of schedule must be replaced, once for the adsorbed vaccine for diphtheria, tetanus and acellular pertussis.
	Human Papillomavirus : quadrivalent recombinant vaccine against HPV (types 6, 11, 16 e 18): at least two doses with a distance of 6 months between them for both sexes patients from 9 to 26 years.
	Hepatitis A: non immune patients must receive two dose series of vaccine, with an interval of 6 to 12 months, from the first to the second dose.
	Hepatitis B: non immune patients must receive three doses, on 0, 1st and 6th month***.
	Meningococcus: Meningococcal quadrivalent conjugate vaccine – two doses for teenagers with an interval of 5 years and Just one dose for adults, directed for specific groups (recruited soldiers, people living or traveling to endemic areas, as well as those welcomed in crowded bedrooms, or with complement deficiency or asplenic.
Attenuated vaccines to be used in IBD patients, if it is not planned yet to start immunosuppressive therapy	Triple viral vaccine: two doses with 30 days of interval between them.
	Varicella: two doses in adults, with 4 to 8 weeks between them, if patients are not immune.
	Herpes zoster: one dose in patients ≥ 50 -60 years.
	Yellow Fever: one dose if patient not vaccinated previously.

** Ideally it must start with application of VPC13 followed by one dose of VPP23 after 8 weeks in immunosuppressed patients or 6 to 12 weeks in immunocompetent. A second dose of VPP 23 should be administered after 5 years since the first dose. *** If immunomodulator or biologic therapy is urgent, it is possible to decrease the interval between doses to 0, 1 and 2 months and evaluate the anti – HBs status after 1 to 2 months to define the immunoprotection; serum levels below 10 mIU/mL are considered insufficient and patients need another schedule with double dose in each application. Alternatively, in this last circumstance it can be used the associated anti – HAV and anti – HBV vaccine. *Adapted from references [72,75,78,80].

tients^[86]. On the other hand, the pegol certolizumab is a pegylated humanized antibody Fab fragment against TNF, and as such lacks an Fc receptor, and, therefore, it may not be necessary to discontinue it during pregnancy^[86].

Although biologics have been detected in breast milk in little amounts, the extent to which they are absorbed by the infant is unclear^[82]. Recent studies support the safety of continuing immunomodulators and anti-tumor necrosis factor agents during breastfeeding^[87].

SUMMARY

Suitable patient's selection, counseling and education are all important matter for the successful use of biologics on IBD patients. A cornerstone to provide appropriate treatment with biologics is to confirm that active IBD is present. Furthermore, it is paramount that other conditions with overlapping clinical presentations must be excluded, including IBS, underlying bacterial or viral infection, among other sickness. A detailed history should be gathered to evaluate for contraindications to biological therapy. Prior to starting biologics, the patients need to be screened for latent tuberculosis, hepatitis B and C viruses, and HIV infection. Additionally, clinicians must stay vigilant about the risk of reactivation of infectious tropical diseases during biological therapy in patients migrating or travelling from tropical endemic areas. Preferentially, vaccination status should be checked and updated upon diagnosis of IBD prior to the using immunosuppressant. Current guidelines recommend that adults with IBD follow the same routine immunization schedule as healthy one, avoiding live vaccines during immunosuppressive therapy. Likewise, patients who receive live virus vaccines should wait at least one month to receive biologic therapy. They also should be instructed that biologics use must be stopped and to seek a medical care service in case of new onset and persistence of symptoms during treatment. To date, biological agents have demonstrated a favorable safety profile in IBD patients with benefits usually outweighing the risks, but in clinical practice, this issue should be evaluated and discussed on a case-by-case basis with each individual patient.

AUTHOR CONTRIBUTIONS

Chebli JMF, Gaburri PD, and Chebli LA designed the concept for this review; Furtado MCV, Aguiar NP, Ribeiro TCR, Malaguti C performed the literature search; Ribeiro TCR, Costa LA, Chebli JMF analyzed the data; Furtado MCV, Aguiar NP, Ribeiro TCR, Malaguti C, Chebli LA, Gaburri PD and Chebli JMF composed the paper and revised the manuscript; Furtado MCV, Gaburri PD, Costa LA, Chebli JMF assisted with editing the manuscript. All authors approved the final version.

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REFERENCES

1. Park SH, Aniwan S, Loftus EV Jr. Advances in the use of biologics and other novel drugs for managing inflammatory bowel disease. *Curr Opin Pharmacol* 2017; **37**: 65-71. [DOI: 10.1016/j.coph.2017.09.007].
2. de Souza GS, Vidigal FM, Chebli LA, da Rocha Ribeiro TC, Furtado MC, de Lima Pace FH, de Miranda Chaves LD, de Oliveira Zanini KA, Gaburri PD, de Azevedo Lucca F, Zanini A, Ribeiro LC, Chebli JM. Effect of azathioprine or mesalazine therapy on incidence of re-hospitalization in sub-occlusive ileocecal Crohn's disease patients. *Med Sci Monit* 2013; **19**: 716-722. [DOI: 10.12659/MSM.889196].
3. Peyrin-Biroulet L, Panés J, Sandborn WJ, Vermeire S, Danese S, Feagan BG, Colombel JF, Hanauer SB, Rycroft B. Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. *Clin Gastroenterol Hepatol* 2016; **14**: 348-354.e17. [DOI: 10.1016/j.cgh.2015.06.001].
4. Santos JCD, Malaguti C, Lucca FA, Cabalzar AL, Ribeiro TCDR, Gaburri PD, Chebli LA, Chebli JMF. Impact of biological therapy on body composition of patients with Chron's disease. *Rev Assoc Med Bras* 2017; **63**: 407-413. [DOI: 10.1590/1806-9282.63.05.407].
5. Peyrin-Biroulet L, Fiorino G, Buisson A, Danese S. First-line therapy in adult Crohn's disease: who should receive anti-TNF agents? *Nat Rev Gastroenterol Hepatol* 2013; **10**: 345-351. [DOI: 10.1038/nrgastro.2013.31].
6. Pouillon L, Bossuyt P, Peyrin-Biroulet L. Considerations, challenges and future of anti-TNF therapy in treating inflammatory bowel disease. *Expert Opin Biol Ther* 2016; **16**: 1277-1290. [DOI: 10.1080/14712598.2016.1203897].
7. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, Peyrin-Biroulet L, Cullen GJ, Daperno M, Kucharzik T, Rieder F, Almer S, Armuzzi A, Harbord M, Langhorst J, Sans M, Chowers Y, Fiorino G, Juillerat P, Mantzaris GJ, Rizzello F, Vavricka S, Gionchetti P; ECCO. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017; **11**: 3-25. [DOI: 10.1093/ecco-jcc/jjw168].
8. Chebli JM, Gaburri PD, Chebli LA, da Rocha Ribeiro TC, Pinto AL, Ambrogini Júnior O, Damião AO. A guide to prepare patients with inflammatory bowel diseases for anti-TNF- α therapy. *Med Sci Monit* 2014; **20**: 487-498. [DOI: 10.12659/MSM.890331].
9. Lahiff C, Safaie P, Awais A, Akbari M, Gashin L, Sheth S, Lembo A, Leffler D, Moss AC, Cheifetz AS. The Crohn's disease activity index (CDAI) is similarly elevated in patients with Crohn's disease and in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2013; **37**: 786-794. [DOI: 10.1111/apt.12262].
10. Kane SV. Preparing for biologic or immunosuppressant therapy. *Gastroenterol Hepatol* 2011; **7**: 544-546. [PMID: 22298992].
11. Schoepfer AM, Beglinger C, Straumann A, Safroneeva E, Romero Y, Armstrong D, Schmidt C, Trummel M, Pittet V, Vavricka SR. Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. *Inflamm Bowel Dis* 2013; **19**: 332-341. [DOI: 10.1097/MIB.0b013e3182810066].
12. Schoepfer AM, Beglinger C, Straumann A, Trummel M, Vavricka SR, Bruegger LE, Seibold F. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol* 2010; **105**: 162-169. [DOI: 10.1038/ajg.2009.545].
13. Mosli MH, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, Sandborn WJ, Feagan BG. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2015; **110**: 802-819. [DOI: 10.1038/ajg.2015.120].
14. Quigley EM. Overlapping irritable bowel syndrome and inflammatory bowel disease: less to this than meets the eye? *Therap Adv Gastroenterol* 2016; **9**(2): 199-212. [DOI: 10.1177/1756283X15621230].
15. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease:

- systematic review and meta-analysis. *Am J Gastroenterol* 2012; **107**: 1474-1482. [DOI: 10.1038/ajg.2012.260].
16. Camilleri M. Managing symptoms of irritable bowel syndrome in patients with inflammatory bowel disease. *Gut* 2011; **60**: 425-428. [DOI: 10.1136/gut.2010.234583].
 17. Meng J, Agrawal A, Whorwell PJ. Refractory inflammatory bowel disease-could it be an irritable bowel? *Nat Rev Gastroenterol Hepatol* 2013; **10**: 58-61. [DOI: 10.1038/nrgastro.2012.173].
 18. Chebli JM, de Abreu NC, Chebli LA, Reboredo MM, Pinheiro HS. Intestinal spirochetosis: an unusual cause of IBD flare-up during anti-TNF therapy. *Int J Colorectal Dis* 2016; **31**: 745-746. [DOI: 10.1007/s00384-015-2240-8].
 19. Rao K, Higgins PD. Epidemiology, Diagnosis, and Management of *Clostridium difficile* Infection in Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2016; **22**: 1744-1754. [DOI: 10.1097/MIB.0000000000000793].
 20. Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gece KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagórowicz E, Raine T, Harbord M, Rieder F; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis* 2017; **11**: 649-670. [DOI: 10.1093/ecco-jcc/jjx008].
 21. Sager K, Alam S, Bond A, Chinnappan L, Probert CS. Review article: cytomegalovirus and inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; **41**: 725-733. [DOI: 10.1111/apt.13124].
 22. Ricci JE Júnior, Chebli LA, Ribeiro TC, Castro AC, Gaburri PD, Pace FH, Barbosa KV, Ferreira LE, Passos MD, Malaguti C, Delgado AH, Campos JD, Coelho AR, Chebli JM. Small-Intestinal Bacterial Overgrowth is Associated With Concurrent Intestinal Inflammation But Not With Systemic Inflammation in Crohn's Disease Patients. *J Clin Gastroenterol* 2017 Jan 27. [DOI: 10.1097/MCG.0000000000000803].
 23. Di Sario A, Bendia E, Schiada L, Sassaroli P, Benedetti A. Biologic Drugs in Crohn's Disease and Ulcerative Colitis: Safety Profile. *Curr Drug Saf* 2016; **11**: 55-61. [DOI: 10.2174/157488631101160212171757].
 24. Cohn HM, Dave M, Loftus EV Jr. Understanding the Cautions and Contraindications of Immunomodulator and Biologic Therapies for Use in Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2017; **23**: 1301-1315. [DOI: 10.1097/MIB.0000000000001199].
 25. Siegel CA. Shared decision making in inflammatory bowel disease: helping patients understand the tradeoffs between treatment options. *Gut* 2012; **61**: 459-465. [DOI: 10.1136/gutjnl-2011-300988].
 26. Annese V, Beaugerie L, Egan L, Biancone L, Bolling C, Brandts C, Dierickx D, Dummer R, Fiorino G, Gornet JM, Higgins P, Katsanos KH, Nissen L, Pellino G, Rogler G, Scaldaferrri F, Szymanska E, Eliakim R; ECCO. European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. *J Crohns Colitis* 2015; **9**: 945-965. [DOI: 10.1093/ecco-jcc/jjv141].
 27. Cosnes J. What Should Be Done in Inflammatory Bowel Disease Patients with Prior Malignancy? *Dig Dis* 2017; **35**: 50-55. [DOI: 10.1159/000449083].
 28. Siegel CA. Review article: explaining risks of inflammatory bowel disease therapy to patients. *Aliment Pharmacol Ther* 2011; **33**: 23-32. [DOI: 10.1111/j.1365-2036.2010.04489.x].
 29. Ardura SST Monica I, Siegel Jane D, Lu Ying, Bousvaros Athos, Crandall Wallace. NASPGHAN clinical report: surveillance, diagnosis, and prevention of infectious diseases in pediatric patients with inflammatory bowel disease receiving tumor necrosis factor-alfa inhibitors. *J Pediatr Gastroenterol Nutr* 2016; **63**: 130-155. [DOI: 10.1097/MPG.0000000000001188].
 30. Cosnes J. Smoking and Diet: Impact on Disease Course? *Dig Dis* 2016; **34**(1-2): 72-77. [DOI: 10.1159/000442930].
 31. Abreu C, Sarmiento A, Magro F. Screening, prophylaxis and counselling before the start of biological therapies: A practical approach focused on IBD patients. *Dig Liver Dis* 2017; **49**(12): 1289-1297. [DOI: 10.1016/j.dld.2017.09.002].
 32. Park SH, Aniwani S, Loftus EV Jr. Advances in the use of biologics and other novel drugs for managing inflammatory bowel disease. *Curr Opin Pharmacol* 2017; **37**: 65-71. [DOI: 10.1016/j.coph.2017.09.007].
 33. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, Peyrin-Biroulet L, Cullen GJ, Daperno M, Kucharzik T, Rieder F, Almer S, Armuzzi A, Harbord M, Langhorst J, Sans M, Chowers Y, Fiorino G, Juillerat P, Mantzaris GJ, Rizzello F, Vavricka S, Gionchetti P; ECCO. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017; **11**: 3-25. [DOI: 10.1093/ecco-jcc/jjw168].
 34. Bartalesi F, Scirè C, Requena-Méndez A, Abad MA, Buonfrate D, Caporali R, Conti F, Diaz-Gonzalez F, Fernández-Espartaco C, Martínez-Fernández C, Mascarello M, Generali E, Minisola G, Morrone A, Muñoz J, Richi P, Sakellariou G, Salas Coronas J, Spinicci M, Castelli F, Bartoloni A, Bisoffi Z, Gimenez-Sanchez F, Muñoz-Fernandez S, Matucci-Cerinic M. Recommendations for infectious disease screening in migrants to Western Europe with inflammatory arthropathies before starting biologic agents. Results from a multidisciplinary task force of four European societies (SIR, SER, SIMET, SEMTSI) facing the largest impact of the flow of migrants today. *Clin Exp Rheumatol* 2017; **35**: 752-765. [PMID: 28516869].
 35. Park DI, Hisamatsu T, Chen M, Ng SC, Ooi CJ, Wei SC, Banerjee R, Hilmi IN, Jeon YT, Han DS, Kim HJ, Ran Z, Wu K, Qian J, Hu PJ, Matsuoka K, Andoh A, Suzuki Y, Sugano K, Watanabe M, Hibi T, Puri AS, Yang SK. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 1: risk assessment. *J Gastroenterol Hepatol* 2018; **33**(1): 20-29. [DOI: 10.1111/jgh.14019].
 36. Dobler CC. Biologic Agents and Tuberculosis. *Microbiol Spectrum* 2016; **4**(6): 1-10. [DOI: 10.1128/microbiolspec.TNM17-0026-2016].
 37. Abreu C, Afonso J, Camila Dias C, Ruas R, Sarmiento A, Magro F. Serial Tuberculosis Screening in Inflammatory Bowel Disease Patients Receiving Anti-TNF α Therapy. *J Crohns Colitis* 2017; **11**(10): 1223-1229. [DOI: 10.1093/ecco-jcc/jjx080].
 38. Wallis RS. Infectious complications of tumor necrosis factor blockade. *Curr Opin Infect Dis* 2009; **22**: 403-409. [DOI: 10.1097/QCO.0b013e32832dda55].
 39. Abreu C, Almeida F, Ferraz R, Dias CC, Sarmiento A, Magro F. The tuberculin skin test still matters for the screening of latent tuberculosis infections among Inflammatory Bowel Diseases patients. *Dig Liver Dis* 2016; **48**: 1438-1443. [DOI: 10.1016/j.dld.2016.08.107].
 40. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero D, Pascual-Gómez E, Mola EM, Carreño L, Figueroa M; BIOBADASER Group. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum* 2005; **52**: 1766-1772. [DOI: 10.1002/art.21043].
 41. Diel R, Loddenkemper R, Nienhaus A. Evidence-based comparison of commercial interferon-gamma release assays for

- detecting active TB: a metaanalysis. *Chest* 2010; **137**: 952-968. [DOI: 10.1378/chest.09-2350].
42. Cotter J, Rosa B. The importance of IGRA in patients candidates for biological therapy. *J Crohns Colitis* 2013; **7**: 928-929. [DOI: 10.1016/j.crohns.2013.02.013].
 43. Duarte R, Campinha S, Cotter J, Rosa B, Varela P, Correia A, Canhão H, Fonseca JE; Portuguese Society of Pulmonology; Portuguese Society of Gastroenterology; Portuguese Society of Dermatology and Venereology; Portuguese Society of Rheumatology. Position paper on tuberculosis screening in patients with immune mediated inflammatory diseases candidates for biological therapy. *Acta Reumatol Port* 2012; **37**: 253-259. [PMID: 23348114].
 44. 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. [DOI: 10.1111/j.1365-2036.2007.03553.x]
 45. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement: *Am J Respir Crit Care Med* 2000; **161**(4 Pt 2): S221-S247. [DOI: 10.1164/ajrccm.161.supplement_3.ats600]
 46. Degasperi E, Caprioli F, El Sherif O, Back D, Colombo M, Aghemo A. Challenges in treating patients with inflammatory bowel disease and concurrent viral hepatitis infection. *Expert Rev Gastroenterol Hepatol* 2016; **10**: 1373-1383. [DOI: 10.1080/17474124.2016.1246181]
 47. Dusheiko G. Treatment of HBeAg positive chronic hepatitis B: interferon or nucleoside analogues. *Liver Int* 2013; **33**: 137-150. [DOI: 10.1111/liv.12078].
 48. 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; GETECCU (Grupo Español de Enfermedades de Crohn y Colitis Ulcerosa). 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. [DOI: 10.1038/ajg.2008.4].
 49. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007; **45**: 507-539. [DOI: 10.1002/hep.21513].
 50. 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, Vîget N, Yazdanpanah Y, Eliakim R, Colombel JF; European Crohn's and Colitis Organisation (ECCO). Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014; **8**(6): 443-468. [DOI: 10.1016/j.crohns.2013.12.013].
 51. 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-Carballeira M, Fernández-Bañares F, Viver JM, Esteve M; REPENTINA study; GETECCU (Grupo Español de Enfermedades de Crohn y Colitis Ulcerosa) Group. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. *Gut* 2010; **59**(10): 1340-1346. [DOI: 10.1136/gut.2010.208413].
 52. Loras C, Gisbert JP, Saro MC, Piqueras M, Sánchez-Montes C, Barrio J, Ordás I, Montserrat A, Ferreiro R, Zabana Y, Chaparro M, Fernández-Bañares F, Esteve M; REPENTINA study, GETECCU group (Grupo Español de trabajo de Enfermedades de Crohn y Colitis Ulcerosa). Impact of surveillance of hepatitis b and hepatitis c in patients with inflammatory bowel disease under anti-TNF therapies: multicenter prospective observational study (REPENTINA 3). *J Crohns Colitis* 2014; **8**(11): 1529-1538. [DOI: 10.1016/j.crohns.2014.06.009].
 53. Belle A, Baumann C, Bigard MA, Zallot C, Gizard E, Guéant JL, Bronowicki JP, Peyrin-Biroulet L. Impact of immunosuppressive therapy on hepatitis B vaccination in inflammatory bowel diseases. *Eur J Gastroenterol Hepatol*. 2015; **27**(8): 877-881. [DOI: 10.1097/MEG.0000000000000370].
 54. Farraye FA. Vaccination of Patients with Inflammatory Bowel Disease. *Gastroenterol Hepatol* 2017; **3**: 431-434. [PMID: 28867973].
 55. Rojas-Feria M, Castro M, Suárez E, Ampuero J, Romero-Gómez M. Hepatobiliary manifestations in inflammatory bowel disease: the gut, the drugs and the liver. *World J Gastroenterol* 2013; **19**(42): 7327-7340. [DOI: 10.3748/wjg.v19.i42.7327].
 56. Seto WK, Wong DK, Chan TS, Hwang YY, Fung J, Liu KS, Gill H, Lam YF, Cheung KS, Lie AK, Lai CL, Kwong YL, Yuen MF. Association of Hepatitis B Core-Related Antigen With Hepatitis B Virus Reactivation in Occult Viral Carriers Undergoing High-Risk Immunosuppressive Therapy. *Am J Gastroenterol* 2016; **111**(12): 1788-1795. [DOI: 10.1038/ajg.2016.436].
 57. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**(2): 370-398. [DOI: 10.1016/j.jhep.2017.03.021].
 58. López-Serrano P, Pérez-Calle JL, Sánchez-Tembleque MD. Hepatitis B and inflammatory bowel disease: role of antiviral prophylaxis. *World J Gastroenterol* 2013; **19**: 1342-1348. [DOI: 10.3748/wjg.v19.i9.1342].
 59. 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].
 60. Raimondo G, Allain JP, Brunetto MR, Buendia MA, Chen DS, Colombo M, Craxi A, Donato F, Ferrari C, Gaeta GB, Gerlich WH, Levrero M, Locarnini S, Michalak T, Mondelli MU, Pawlotsky JM, Pollicino T, Prati D, Puoti M, Samuel D, Shouval D, Smedile A, Squadrito G, Trépo C, Villa E, Will H, Zanetti AR, Zoulim F. Statements from the Taormina expert meeting on occult hepatitis B virus infection. *J Hepatol* 2008; **49**(4): 652-657. [DOI: 10.1016/j.jhep.2008.07.014].
 61. Shouval D, Shibolet O. Immunosuppression and HBV reactivation. *Semin Liver Dis* 2013; **33**: 167-177. [DOI: 10.1055/s-0033-1345722].
 62. Allen AM, Kim WR, Larson J, Loftus EV Jr. Efficacy and safety of treatment of hepatitis C in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; **11**: 1655-1660. [DOI: 10.1016/j.cgh.2013.07.014].
 63. Sansone S, Guarino M, Castiglione F, Rispo A, Auriemma F, Loperto I, Rea M, Caporaso N, Morisco F. Hepatitis B and C virus reactivation in immunosuppressed patients with inflammatory bowel disease. *World J Gastroenterol* 2014; **20**(13): 3516-3524. [DOI: 10.3748/wjg.v20.i13.3516].
 64. Campbell S, Ghosh S. Infliximab therapy for Crohn's disease in the presence of chronic hepatitis C infection. *Eur J Gastroenterol Hepatol* 2001; **13**: 191-192. [PMID: 11246620].
 65. European Association for Study of Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol* 2016; **66**: 153-194. [DOI: 10.1016/j.jhep.2016.09.001].
 66. Peyrin-Biroulet L, Cadranet JF, Noursbaum JB, Oussalah A,

- Seddik M, Canva V, Cortot A, Sogni P, Gueant JL, Bigard MA, Roblin X, Bronowicki JP. Interaction of ribavirin with azathioprine metabolism potentially induces myelosuppression. *Aliment Pharmacol Ther* 2008; **28**(8): 984-993. [DOI: 10.1111/j.1365-2036.2008.03812.x].
67. Pasquereau S, Kumar A, Herbein G. Targeting TNF and TNF Receptor Pathway in HIV-1 Infection: from Immune Activation to Viral Reservoirs. *Viruses* 2017; **9**(4). [DOI: 10.3390/v9040064].
 68. Ting PT, Koo JY. Use of etanercept in human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) patients. *Int J Dermatol* 2006; **45**: 689-692.
 69. Gaylis, N. Infliximab in the treatment of an HIV positive patient with Reiter's syndrome. *J Rheumatol* 2003; **30**: 407-411. [PMID: 12563704].
 70. Gallitano SM, McDermott L, Brar K, Lowenstein E. Use of tumor necrosis factor (TNF) inhibitors in patients with HIV/AIDS. *J Am Acad Dermatol* 2016; **74**: 974-980. [DOI: 10.1016/j.jaad.2015.11.043].
 71. Wangsiricharoen S, Ligon C, Gedmintas L, Dehrab A, Tung-siripat M, Bingham C, Lozada C, Calabrese L. The rates of serious infections in HIV-infected patients who received tumor necrosis factor (TNF)- α inhibitor therapy for concomitant autoimmune diseases. *Arthritis Care Res* 2016; **69**: 449-452. [DOI: 10.1002/acr.22955].
 72. Long MD, Gulati A, Wohl D, Herfarth H. Immunizations in Pediatric and Adult Patients with Inflammatory Bowel Disease: A Practical Case-based Approach. *Inflamm Bowel Dis* 2015; **21**(8): 1993-2003. [DOI: 10.1097/MIB.0000000000000395].
 73. Gisbert JP, Chaparro M. Vaccination strategies in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 277-285. [DOI: 10.1038/nrgastro.2013.28].
 74. Kantso B, Simonsen J, Hoffmann S, Valentiner-Branth P, Petersen AM, Jess T. Inflammatory bowel disease patients are at increased risk of invasive pneumococcal disease: a nationwide Danish cohort study 1977-2013. *Am J Gastroenterol* 2015; **110**: 1582-1587. [DOI: 10.1038/ajg.2015.284].
 75. Reich J, Wasan SK, and Farraye FA. Vaccination and Health Maintenance Issues to Consider in Patients With Inflammatory Bowel Disease. *Gastroenterol Hepatol* 2017; **13**,717-25. [PMID: 29339947].
 76. Melmed GY. Vaccination strategies for patients with inflammatory bowel disease on immunomodulators and biologics. *Inflamm Bowel Dis* 2009; **15**: 1410-1416. [DOI: 10.1002/ibd.20943].
 77. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, Kang I; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014; **58**(3): 309-318. [DOI: 10.1093/cid/cit816].
 78. Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. *Am J Gastroenterol* 2017; **112**: 241-258. [DOI: 10.1038/ajg.2016.537].
 79. Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC): Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2008; **57**(RR-5): 1-30. [PMID: 18528318].
 80. Tomczyk S, Bennett NM, Stoecker C, Gierke R, Moore MR, Whitney CG, Hadler S, Pilishvili T; Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥ 65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2014; **63**: 822-825. [PMID: 25233284].
 81. Dipasquale V, Romano C. Vaccination strategies in pediatric inflammatory bowel disease. *Vaccine* 2017; **35**(45): 6070-6075. [DOI: 10.1016/j.vaccine.2017.09.031].
 82. Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. *Am J Gastroenterol* 2013; **108**: 1426-1438. [DOI: 10.1038/ajg.2013.171].
 83. Lu Y, Bousvaros A. Immunizations in children with inflammatory bowel disease treated with immunosuppressive therapy. *Gastroenterol Hepatol* 2014; **10**: 355-363. [PMID: 25013388].
 84. Veereman-Wauters G, de Ridder L, Veres G, Kolacek S, Fell J, Malmborg P, Koletzko S, Dias JA, Misak Z, Rahier JF, Escher JC; ESPGHAN IBD Porto Group. Risk of infection and prevention in pediatric patients with IBD: ESPGHAN IBD Porto Group commentary. *J Pediatr Gastroenterol Nutr* 2012; **54**(6): 830-837. [DOI: 10.1097/MPG.0b013e31824d1438].
 85. Mahadevan U, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, Ullman T, Glover S, Valentine JF, Rubin DT, Miller J, Abreu MT. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; **11**(3): 286-292. [DOI: 10.1016/j.cgh.2012.11.011].
 86. Mahadevan U, McConnell RA, Chambers CD. Drug Safety and Risk of Adverse Outcomes for Pregnant Patients With Inflammatory Bowel Disease. *Gastroenterology* 2017; **152**(2): 451-462.e2. [DOI: 10.1053/j.gastro.2016.10.013].
 87. Gaidos JK, Kane SV. Managing IBD Therapies in Pregnancy. *Curr Treat Options Gastroenterol* 2017; **15**(1): 71-83. [DOI: 10.1007/s11938-017-0123-5].