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CONSENSUS/GUIDELINES

Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease

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1. Introduction

The treatment of inflammatory bowel disease (IBD) has been revolutionised over the past decade by the increasing use of immunomodulators. With such immunomodulation, the potential for opportunistic infection is a key safety concern for patients with IBD. Opportunistic infections pose particular problems for the clinician: they are often difficult to recognise and are associated with appreciable morbidity or mortality, because they are potentially serious and hard to treat effectively. This led the European Crohn's and Colitis Organisation (ECCO) to update the previous Consensus meeting on opportunistic infections in IBD. To organise the work, infections were classified into six major topics. Guideline statements of 2009 were analysed systematically by the chairs and the working parties. In parallel, the working parties performed a systematic literature search of their topic with the appropriate key words using Medline/Pubmed and the Cochrane database, as well as their own files. The evidence level (EL) was graded according to the 2011 Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653). Provisional update guideline statements were then posted on a weblog. Discussions and exchange of the literature evidence among the working party members was then performed on the weblog. The working parties then met in Lille on the 15th–16th of November 2012 to agree on the statements. Consensus was defined as agreement by >80% of participants, termed a Consensus Statement and numbered for convenience in the document.

This paper is the product of work by gastroenterologists, infectious disease experts and pediatricians. It provides guidance on the prevention, detection and management of opportunistic infections in patients of all age categories with IBD. After a section on definitions and risk factors for developing opportunistic infection, there are five sections on different infectious agents, followed by a section on information and guidance for patients with IBD travelling frequently or to less economically developed countries. In the final section, a systematic work up and vaccination programme is proposed for consideration in patients exposed to immunomodulator therapies.

The final document on each topic was written by the workgroup leader and their working party. Statements are intended to be read in context with qualifying comments and not read in isolation. The final text was edited for consistency of style by JF Rahier, F Magro, R Eliakim and JF Colombel before being circulated and approved by the participants. In some areas the level of evidence is generally low, which reflects the paucity of randomised controlled trials. Consequently expert opinion is included where appropriate.

2. Definitions and risk factors

2.1. Definition of an immunocompromised patient

An immunocompromised host has an alteration in phagocytic, cellular, or humoral immunity that increases the risk of an infectious complication or an opportunistic process. Patients may also be immunocompromised if they have a breach of their skin or mucosal defense barriers that permits microorganisms to cause either local or systemic infection.[1] There is no clearcut definition of an immunocompromised state. Three categories are recognised by the Centers for Disease Control,[2] depending on the severity of immunosuppression:

1. Persons who are severely immunocompromised not as a result of HIV infection: Severe immunosuppression can be the result of congenital immunodeficiency, leukemia, lymphoma, generalised malignancy or therapy with alkylating agents, antimetabolites, radiation, or high doses of corticosteroids (2 mg/kg body weight, or >20 mg/day of prednisolone, Section 2.4.1)
2. Persons with HIV infection
3. Persons with conditions that cause limited immune deficits (e.g. hyposplenism and renal failure)

2.2. Definition of opportunistic infection

An opportunistic infection may be defined as a usually progressive infection by a microorganism that has limited (or no) pathogenic capacity under ordinary circumstances, but which is able to cause serious disease as a result of the predisposing effect of another disease or of its treatment.[3]

2.3. What makes an IBD patient immunocompromised?

ECCO Statement OI 2A

Patients with IBD should not be routinely considered to have altered immunocompetence [EL5] per se, despite evidence of impaired innate mucosal immunity. Different immunomodulators may alter immune responsiveness by different mechanisms and to varying degrees, but there is currently no single method of evaluating the effects of immunosuppression on the immune system [EL5]

From genome wide association studies there is increasing evidence of an aberrant immune response in IBD.[4] Susceptibility loci involve both the innate and adaptive immune response towards a diminished diversity of commensal microbiota.[5] Description of the numerous mechanisms contributing to this dysimmunity is beyond the scope of this article. Despite evidence of defective mucosal immunity, there is no proof of a systemic immune defect in patients with IBD in the absence of concomitant immunomodulator therapy.

Patients with IBD are therefore rendered immunocompromised through their treatment. Immunomodulators commonly used in inflammatory bowel disease are corticosteroids, thiopurines, methotrexate, calcineurin inhibitors, anti-tumor necrosis factor agents, or other biologics. Their modes of action differ, but they all compromise to some extent the patient's immune response. To date there is no accurate biological means to quantify immunosuppression in patients with IBD.

2.4. Risk factors for developing an opportunistic infection

ECCO Statement OI 2C

The immunomodulators commonly used in IBD and associated with an increased risk of infections include corticosteroids, thiopurines, methotrexate, calcineurin inhibitors, anti-TNF agents and other biologics [EL1]. For corticosteroids, a total daily dose equivalent to $\geq$20 mg of prednisolone for $\geq$2 weeks is associated with an increased risk of infections [EL3]

Predisposing factors not only lower the patient's resistance to opportunistic infection, but enable the infection to develop and progress to an extent that is not otherwise seen.[3] Only few data are available regarding risks factors for developing an opportunistic infection. In a recent study infection-related hospitalisations were independently associated with age, co-morbidity, malnutrition, total parenteral nutrition, and bowel surgery.[6] Information was therefore also collected from patients with rheumatological disease and from the general population. We have defined two categories of risk: those that are external to the patient (immunomodulator therapy, exposure to pathogens, or geographic clustering) and those that are inherent to the patient (age, comorbidity and malnutrition).

2.4.1. Immunomodulator therapy

ECCO Statement OI 2B

IBD patients at risk of opportunistic infections are those treated with immunomodulators [EL1], especially in combination [EL3], and those with malnutrition [EL5]. In addition, co-morbidities and a history of serious infections should be considered. Age is an independent risk factor for opportunistic infections in IBD [EL3]

Viral, bacterial, parasitic and fungal infections have all been associated with the use of immunomodulator therapy in IBD. Despite different mechanisms of action, any of those drugs can lead to any type of infection. No strict correlation between a specific immunomodulator drug and a certain type of infection has been observed. Toruner and colleagues found that corticosteroid use was more commonly associated with fungal (Candida spp.) infections, azathioprine with viral infections and anti-TNF therapy with fungal or mycobacterial infections.[7] There was, however, considerable overlap. Furthermore, these drugs are commonly prescribed together, so the infectious event might be the consequence of cumulative immunosuppressive activity.

Data that identify immunomodulators as risk factors for opportunistic infection come mainly from the rheumatologic literature.[8] Corticosteroids are dose dependently linked to increased risk of both serious[9,10] and non-serious infections (NSI) in rheumatoid arthritis (RA).[11] Relative risks for NSIs in one study were 1.10 and 1.85 with prednisolone dosed at $<$5 mg/d and $>$20 mg/d respectively.[11] In the CORRONA registry the RR for all infectious events was increased with $>$10 mg/d (RR 1.30) whilst any dose increased the risk of opportunistic infection (RR 1.67).[12] There are no precise data in the IBD population that identify a dose associated with increased risk of infection. The risk of post-operative infections has been linked to concurrent use of corticosteroids in IBD patients undergoing elective surgery.[13] Both corticosteroids and anti-TNF therapy independently, and more significantly

in combination, increased the risks of post-operative intra-abdominal infectious complications in a retrospective study of 3 referral centres.[14] In this setting, a recent meta-analysis has shown anti-TNF therapy to increase post-operative infectious complications in Crohn's disease (OR 1.45) but not ulcerative colitis.[15] However, a different group of authors did not demonstrate an increased risk with anti-TNF therapy for all post-operative complications.[16]

Anti-TNF therapy is associated with increased rates of serious bacterial infection in RA, especially in the first 6 months of treatment initiation.[17] Rates of opportunistic infections, serious infections and of septic arthritis were increased in anti-TNF treated RA patients as reported in the CORRONA, RABBIT and British Society for Rheumatology biologics registries respectively.[10,12,18] The TREAT registry showed an increased risk of serious infections with anti-TNF therapy in Crohn's disease (hazard ratio 1.47), albeit less than that for corticosteroids (HR 1.57) and narcotics (HR 1.98).[19] A recent meta-analysis of all published data from 22 randomised controlled trials in IBD, demonstrated a 2 fold increased risk of opportunistic infections with anti-TNF therapy.[20]

Each immunomodulator carries an increased risk of infection, although to a varying degree that has not yet been quantified. Of fundamental importance is the observation that combinations of immunomodulator therapy in IBD are associated with an incremental increase in the relative risk of opportunistic infection (three fold increased risk (OR 2.9, 95% CI 1.5–5.3) if any one immunomodulator was used, increasing substantially (OR 14.5, 95% CI 4.9–43) if two or more drugs were used concomitantly).[7]

2.4.2. Exposure to pathogens and geographic clustering

ECCO Statement OI 2D

Exposure to microbial microorganisms is a risk factor for opportunistic infection in the immunocompromised population. Avoiding contact with potential sources including recent recipients of certain live vaccines and travel to endemic areas may reduce the risk of infection in IBD patients on immunomodulators [EL5]

Special consideration should be given to patients from endemic areas, and patients who appear not to be responding to immunomodulators as expected. For pathogens that are ubiquitous, it is impractical to reduce exposure. However, it is logical to avoid high intensity exposure (such as sharing a room with a person, including a child, with active infection or recent recipients of certain live virus vaccines). Living in an area where tuberculosis or other diseases such as histoplasmosis or coccidioidomycosis are endemic, inevitably increases the risk for contracting an opportunistic infection in the normal population, let alone those who are on immunomodulator therapy.[21]

Several microorganisms have been shown to be capable of replicating in water. In addition, both municipal water and ice cubes in drinks have been the source of nosocomial outbreaks of infection. In less economically developed countries, the immunocompromised patient may best be advised to avoid tap water and ice made from tap water.[22]

2.4.3. Age

Immunosenescence is defined as the state of dysregulated immune function that contributes to an increased susceptibility of the elderly to infection and possibly to autoimmune disease and cancer.[23] In this population, there is good evidence of functional alterations in cells from the innate and adaptive immune systems.[24–26] Nevertheless, there is surprisingly little evidence that immune dysregulation has direct relevance to the infections commonly seen in the elderly population, except e.g. reactivation of tuberculosis. On the other hand, there are data to demonstrate that infections with pyogenic bacteria, such as community-acquired pneumonia and urinary tract infections are 3 to 20 fold more prevalent in the elderly than in younger adults. In contrast, viral infections are rare in comparison with the younger population, with the exceptions of influenza, reactivation of herpes zoster and viral gastroenteritis.[24]

In IBD age has been described as an independent risk factor for infection-related hospitalisations.[6] A case-controlled study of 100 patients identified age >50 as a predisposing factor for opportunistic infections (OR 3.0, 95% CI 1.2–7.2 relative to age <25 yr).[7] This finding was supported by Naganuma et al., who also showed an increased incidence of opportunistic infections in patients aged 50 years or older.[25] Along the same line, Cottone et al. described higher rates of severe infections and mortality in patients older than 65 years treated with TNF inhibitors for IBD as compared with younger patients or peers treated without these compounds.[26] Thus, it is of relevance to remain cautious when treating elderly patients with immunosuppressive agents, including TNF inhibitors. Increasing age has also been identified as a significant predictor of infection in a cohort with rheumatoid arthritis.[27]

The available evidence in the paediatric IBD literature shows that immunosuppression increases the risk for infections, but these infections usually seem mild. However, a retrospective study from 20 countries on mortality in paediatric IBD (<19 years) revealed 15 cases who died due to an infection within 5 years.[28] In early life (<1 year of age) severe forms of IBD are distinct clinical entities and may be combined with specific immune defects such as interleukin-10 receptor defects, altered regulatory T cell function and decreased FOXp3 protein levels.[29] These patients are known to develop severe complications such as EBV-induced lymphoproliferative disorder.

2.4.4. Comorbidities

Four comorbidities have been identified as significant risk factors for infection in rheumatoid arthritis patients: chronic lung disease, alcoholism, organic brain disease and diabetes mellitus.[30] In IBD comorbidities have been described in general as an independent risk factor for infection-related hospitalisations,[6] though lacking further specification. Pragmatic caution is advisable when considering immunomodulator therapy in patients with comorbid conditions.

2.4.5. Malnutrition

At malnutrition, the immune system is deprived of the components needed to generate an effective immune response. The immune response can in turn influence nutritional status, since TNFα has a profound influence on nutrient absorption and metabolism.[31] Nutritional deficiency is associated with impaired cell-mediated immunity, as well as decreased phagocyte function, cytokine production, secretory antibody affinity and response, and impairment of the complement system.[32] Immune disorders related to nutritional deficiency range from increased opportunistic infections and cancers to suboptimal responses to vaccinations.[31] Consistent with cause and effect, supplements of micronutrients improve immune responses, reduce the incidence of respiratory infections and ameliorate the impaired response to vaccination.[32]

Nutritional deficiency is common in Crohn's disease and micronutrient deficiency (such as to zinc, copper, or selenium) often go unrecognised. A person at "nutritional risk" is someone whose consumption and/or absorption of specific nutrients is deficient.[31] Numerous factors contribute to malnutrition in IBD: anorexia (due to increased levels of cytokines); drug–nutrient interaction (corticosteroids decrease intestinal absorption and increase renal excretion of calcium; sulfasalazine decreases folate absorption); malabsorption (bacterial overgrowth causing steatorrhoea affects fat-soluble vitamins and B12 absorption); inadequate intake (fear of abdominal pain, or altered taste sensation with metronidazole); reduced caloric intake due to partial small bowel obstruction; ileal resection (vitamin B12); and jejunal disease or resection (iron deficiency), let alone short bowel syndrome.[33] Depressed cellular immunity has been observed in malnourished CD, both in vivo and in vitro.[34] Nevertheless, the correlation between malnutrition and risk of infection has not been extensively studied in IBD. Malnutrition has been described as an independent risk factor for infection-related hospitalisations.[6] Yamamoto et al. found an increased risk of intra-abdominal septic complications in patients with an albumin level <30 g/L.[35] It is still unclear whether this was cause or consequence, since a low serum albumin often reflects decreased synthesis as a consequence of infection or disease activity and is not a good way of assessing malnutrition in IBD patients. By comparison, a low serum total protein or albumin has been associated with opportunistic infection in patients with polymyositis or dermatomyositis.[36]

Better measures of nutritional status are the body mass index (BMI) and the simple expedient of asking a dietitian to conduct a formal nutritional assessment of intake and expenditure. Evaluation is readily achieved when a dietitian is part of the IBD service, conducting a clinic parallel to an IBD clinic. Formal dietetic assessment and nutritional support when starting immunomodulator therapy (or, indeed when considering surgery) in those with a BMI <20 kg/m2 could readily be implemented in clinical practice.

3. Hepatitis C virus (HCV), hepatitis B virus (HBV) and human immunodeficiency virus (HIV)

3.1. Hepatitis C virus infection

> ECCO Statement OI 3A
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> Screening for hepatitis C (HCV) using antibody testing should be considered. If positive, it should be confirmed by detection of HCV RNA. This is important due to the potential risk of worsening liver function as a result of immunosuppressive therapy, concomitant infection with other viruses, (HBV/HIV) or by potentiating the effects of hepatotoxic medications [EL3]. Immunomodulators may influence active chronic HCV (HCVAb+, HCV RNA+) infection. They are not contraindicated but should be used with caution [EL3]. The decision depends on the severity of IBD and the stage of the liver disease. The risk that anti-viral therapy or drug interactions with IBD therapy might exacerbate IBD should be weighed cautiously when considering the need for HCV treatment [EL3]

3.1.1. Background

See supplementary material.

3.1.2. Impact of immunomodulator therapy on the natural history of the disease

The largest series assessing the outcome of HCV infection in patients with IBD and its relation to immunomodulator therapy revealed liver dysfunction in 8/51 HCV RNA positive patients (16%). No cases of HCV RNA reappearance were observed in 23 additional anti-HCV positive patients with negative HCV RNA. Impaired liver function tests were related to corticosteroids given alone and in one case to azathioprine. The severity of hepatic dysfunction was clearly lower for HCV than for HBV although one patient died of liver failure while receiving corticosteroids. This patient also had anti-HBc positive markers without anti-HBs and tested positive for antibodies against HIV, suggesting the existence of an occult HBV infection. Therefore co-infection was probably the cause of fatal outcome.[37] In fact, there is a fairly general agreement in considering HCV infected patients as the category of individuals with the highest prevalence of occult HBV, mainly in Mediterranean and Far East Asian countries.[38] In vitro studies have clearly demonstrated that the HCV "core" protein strongly inhibits HBV replication.[39]

The influence of corticosteroids on HCV-related liver disease progression has been demonstrated in liver

transplant patients in whom steroid boluses are associated with increased viremia, fibrosis progression, and reduced survival. Currently, the only specific recommendation in this setting is the avoidance of overimmunosuppression (particularly corticosteroid boluses). By contrast, progression to liver cirrhosis in immunosuppressed IBD patients seems to be similar to that observed in non-immunosuppressed infected patients.[40] Thus, administration of immunosuppressants, as is common in IBD, does not seem to have a significant detrimental effect on the course of HCV and does not increase progression to end-stage liver disease except for cases of co-infection with HBV and/or HIV in whom severe liver failure may occur.

In addition, a recent systematic review including 37 publications with data on 153 HCV infected patients who were treated with anti-TNF agents, mainly for rheumatoid arthritis, only found one definitely confirmed case of HCV worsening.[41] Moreover, the best evidence that anti-TNF therapy might even be beneficial for HCV infection comes from a study of etanercept as an adjuvant to interferon and ribavirin therapy for naïve patients with chronic HCVinfection.[42] Anti-TNF strategy seems to improve virological response to a combined IFN-α2b/ribavirin therapy in these patients. A small series of hepatitis C patients with arthropathy treated with methotrexate showed no detrimental effect from treatment with methotrexate.[43]

3.1.3. Preventive measures

General measures to reduce or prevent HCV infection are appropriate, since vaccination or chemoprophylaxis for potential infection is not available.

3.1.4. Diagnostic approach, screening and treatment of underlying infection

3.1.4.1. Diagnostic approach and screening. In previous European evidence-based Consensus[44] no agreement could be reached for HCV screening (including HCV antibody testing or HCV PCR in the event of positive antibody testing) prior to starting immunomodulators. Based on present knowledge, showing in some cases a mild liver dysfunction and amplified detrimental effect with other viruses (HBV/HIV) related to immunomodulators, HCV antibody testing and HCV PCR should be determined.

3.1.5. Treatment of the infection

Immunodulators can be used in IBD patients regardless of concomitant HCV infection. On the other hand, antiviral treatment for HCV infection in conjunction with Crohn's disease is generally not recommended, since interferon therapy may worsen disease, although this remains controversial.[45] This is in contrast to ulcerative colitis where interferon therapy does not appear to have an adverse effect.[46] Telaprevir and boceprevir, the HCV protease inhibitors, are inhibitors of the enzyme cytochrome P450 3A, which is responsible for the metabolism of both cyclosporine and tacrolimus. It has recently been demonstrated in healthy volunteers that telaprevir increased the blood concentrations of both cyclosporine and tacrolimus significantly, which could lead to serious or life threatening adverse events.[47] In addition the administration of ribavirin plus interferon or the recently introduced triple antiviral therapy (interferon, rivabirin and protease inhibitors) may increase toxicity of drugs used for IBD maintenance (for example azathioprine, methotrexate). Thus, the risk of IBD worsening by anti-viral therapy or drug interactions with IBD therapy should be cautiously weighted when considering the need of HCV treatment and warrants careful consideration on an individual case basis.

3.1.6. Infection occurring during immunomodulator therapy

There are no reports of acute HCV infection developing during immunomodulator therapy. Interruption of immunomodulator therapy is not necessarily recommended.

3.2. Hepatitis B virus (HBV) infection

ECCO Statement OI 3B

All IBD patients should be tested for HBV (HBsAg, anti-HBAbs, anti-HBcAb) at diagnosis of IBD to determine HBV status. In patients with positive HBsAg, viremia (HBV-DNA) should also be quantified [EL2]

ECCO Statement OI 3C

HBV vaccination is recommended in all HBV anti-HBcAb seronegative patients with IBD. [EL1]. Efficacy of hepatitis B vaccination is impaired in IBD, probably by the disease itself and by anti-TNF drugs. Anti-HBs response should be measured after vaccination. Higher doses of the immunizing antigen may be required to provide protection [EL 2]. Maintenance of HBs antibody should be monitored in patients at risk [EL 5]

ECCO Statement OI 3D

Before, during and for at least 12 months after immunomodulator treatment has ceased, patients who are HBsAg positive (chronic HBV infection) should receive potent anti-viral agents (nucleoside/nucleotide analogues with high barrier to resistance) regardless of the degree of viremia in order to avoid hepatitis B flare [EL2]

ECCO Statement OI 3E

Patients with positive HBcAb and negative HBsAg may have occult HBV infection. Reactivation of occult HBV rarely occurs with immunosuppressive therapy used in IBD [EL2]. Viremia (HBV DNA) should be assessed every 2–3 months but antiviral therapy is not recommended unless HBV-DNA is detected [EL5]

3.2.1. Background

See supplementary material.

3.2.2. Impact of immunomodulator therapy on the natural history of HBV infection in IBD

Reactivation of HBV is a well-described complication of immunosuppression in the setting of organ transplantation or cancer chemotherapy occurring in up to 50% if anti-viral therapy is not administered. Administration of pre-emptive therapy in immunosuppressed patients infected with HBV is well-established by scientific societies.[55] Consequently, the influence of immunomodulators on the course of untreated HBV infection in IBD will never be studied prospectively. The first reported cases of reactivation of HBV in IBD were described after infliximab treatment and have been extensively reviewed elsewhere.[56,57]

However, the majority of these cases were receiving concomitantly other immunomodulators such as corticosteroids or thiopurines, suggesting that more profound immunosuppression may facilitate viral reactivation. Two large retrospective cohort studies assessing the outcome of HBV infection in IBD patients and its relation to immunosuppressive therapy (corticosteroids, immunomodulators, and/or anti-TNFα therapy) have recently been published.[37,58] Liver dysfunction occurred in 25 to 36% of HBsAg-positive IBD patients treated with immunosuppressants. In one of these studies, more than 50% of patients with HBV reactivation had liver failure with one patient dying. The information provided is clinically relevant since the type, duration and combination of immunomodulators differs in IBD from that used in oncological therapy and in other inflammatory conditions requiring immunomodulators. In this regard, most of the HBV-infected patients who had reactivation were receiving treatment with 2 or more immunomodulators for a long period of time, were positive for HBV-DNA and/or had not received prophylactic antiviral treatment.

HBV reactivation was described in a Crohn's disease patient with anti-HBcAb+ and HBsAg− treated with corticosteroids and infliximab.[59] However, reactivation of occult HBV infection seems to be extremely rare with the immunosuppression used in IBD,[37,60] in contrast to patients undergoing oncological chemotherapy, particularly rituximab.[61]

3.2.3. Diagnostic approach, screening, prevention and treatment

All IBD patients have to be tested for HBV infection (HBsAg, anti-Hbs, anti-HBc) to assess infection or vaccination status. In patients presenting with evidence of HBV infection, HBeAg, anti HBe, and HBV DNA should also be assessed.

3.2.3.1. Vaccination in seronegative patients. The burden caused by HBV infection, particularly in IBD, justifies systematic vaccination of all seronegative patients (anti-Hbs− , anti-HBc−). In low endemicity countries the need for universal vaccination has been questioned.[62,63] However, the World Health Organization (WHO) recently recommended the administration of HBV vaccine as soon as possible after birth not only in countries with high endemicity but also in intermediate or low endemicity areas.[64]

The prevalence of HBV infection in IBD is similar than that observed in the reference population.[60,65,66] However, the influx of immigrants from endemic to low prevalence areas may affect HBV prevalence at a local level. In this sense, the expected increased integration of immigrant and indigenous populations may cause transmission of HBV to non-immunised individuals. Moreover, travelers from low to high-risk areas, frequently young people with a low perception of risk, often undertake many high-risk behaviors.

The standard vaccination (rHBAg 20 μg single dose at 0, 1 and 6 months) is ineffective to obtain seroprotection in the majority of non-previously vaccinated IBD patients, particularly in those treated with immunosuppressants.[67–69]

The administrations of accelerated double-dose at 0,1,2 months followed by re-vaccination (0, 1, and 2 months) at a double dose if no adequate response is achieved has demonstrated a better efficacy than the standard schedule (60 to 70% efficacy).[70]

The serological response should be assessed 1 to 2 months after the last dose. Since many patients will lose seroprotection after successful vaccination (18% per patient-year), levels of anti-HBs $>$ 100 IU/l are advisable to achieve adequate seroprotection particularly if anti-TNF treatment is planned.[71] On the other hand, a unique booster dose has demonstrated to restore immune response in pediatric patients who had lost seroprotection and is the recommended schedule in these cases.[72] The frequency of monitoring is not well established but check-ups for anti-HBs yearly or every 2 years seems reasonable mainly in countries with intermediate and high endemicity.

3.2.3.2. Prevention and/or treatment of reactivation in seropositive patients with chronic HBV infection (HBsAg+). In HBsAg+ patients, prophylactic antiviral treatment with nucleotide/nucleoside analogues is recommended, best started 2 weeks prior to the introduction of immunomodulators and continued for 12 months after their withdrawal. Patients with high baseline HBV DNA levels ($>$2000 IU/mL), should continue antiviral treatment until endpoints applicable to immunocompetent patients are reached, according to specific guidelines for HBV treatment.[73,74] A number of case series and study cohorts suggest that nucleotide/nucleoside analogues are safe and effective in IBD patients on immunomodulator treatment.[75] Entecavir and tenefovir are the preferred anti-virals for IBD patients due to their rapid onset of action, highest anti-viral potency and low incidence of resistance. In IBD, a rapid control of HBV infection is required particularly when the administration of immunosuppressants may not be delayed. In addition, the need of long-term immunosuppression requires anti-viral treatments with a high genetic barrier and very low incidence of resistance. Peginterferon-alpha-2a (IFNα) is best avoided for two reasons: first, IFNα may exacerbate Crohn's disease but not ulcerative colitis[46] and second, IFNα may cause additional bone marrow suppression.

3.2.3.3. Prevention of reactivation in seropositive patients with evidence of past HBV infection (HBsAg−, anti-HBcAb+ with or without anti-HBsAb). As previously mentioned, HBV reactivation may occur in patients who are HBsAg-negative but anti-HBc and anti-HBs-positive, as well as in those with isolated anti-HBc.[59] Retrospective and prospective studies[37,60] suggest however that reactivation of occult HBV in IBD rarely occurs. Thus, routine prophylaxis for these individuals is not recommended. These patients should be monitored routinely for elevation of AST/ALT, as well as for

changes in HBV serology and HBV DNA every 1 to 3 months while on immunomodulator therapy based on EASL Clinical Practice Guidelines 2012.[73]

3.2.4. Acute Infection occurring during immunomodulator therapy

There are no reports of newly acquired (acute) HBV infection during immunomodulator or biological therapies. Apart from fulminant hepatitis, where expert opinion has advocated nucleotide/nucleoside treatment, there is no established treatment for acute HBV infection. HBV infection in immunocompetent adults resolves in the vast majority of patients. However immunomodulators might worsen disease or increase the chance of chronic infection. This has been demonstrated for corticosteroids which increase the replication rate of HBV by direct effects on viral replication as well as inhibition of the immune response. In IBD patients with acute HBV infection, immunomodulators and/or biologics should be delayed or stopped until resolution of the acute infection or reactivation (HBV DNA levels $<$ 2000 IU/mL). In these cases nucleotide/nucleoside treatment is recommended in acute infection as it is for HBV reactivation.

3.3. Human immunodeficiency virus (HIV) infection

> ECCO Statement OI 3F
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> Testing for HIV is recommended for adolescent and adult patients with IBD, and should always precede commencement of immunomodulator therapy, based on reports of increased risk and severity of HIV-related infections in patients receiving immunomodulator therapy [EL4]. However, immunomodulators are not necessarily contraindicated in HIV-infected patients [EL4]. Re-testing is indicated for patients at risk [EL 5]

3.3.1. Background

See supplementary material.

3.3.2. Impact of immunomodulator therapy on the natural history of the disease

The effect of corticosteroids on the course of HIV infection in IBD patients has been scarcely studied. Corticosteroids are used as adjunctive therapy in the treatment of complications of HIV infections such as lymphoma or *Pneumocystis jiroveci* infection.[76] A recent observational study demonstrated that patients receiving low-dose prednisolone (5 mg/day) showed significantly lower general cellular immune activation than untreated patients. However, it is unknown if this dose which is clearly lower than that used to treat IBD relapses, has a beneficial effect in HIV disease progression.[77] It is reasonable to use corticosteroids for the therapy of IBD patients with HIV infection receiving HAART who have achieved immune reconstitution and undetectable viral loads, but no data are available. Information regarding the use of azathioprine and its effect on HIV infection in IBD patients is very limited. A case–control study, with a long term follow-up, compared 20 HIV infected IBD patients with 40 non-HIV infected IBD showing lower relapse rates in HIV infected patients than in non-infected ones. Six HIV infected patients were receiving azathioprine without any reported adverse outcome. The majority of these patients were receiving HAART therapy.[78]

TNF-α has been implicated in the pathogenesis of HIV infection, by contributing to HIV replication through activation of NF-κB.[79] Increased TNF-α concentrations have also been associated with advanced stages of HIV infection and the occurrence of infectious complications. It has also been proposed that increased circulating TNF-α, interpreted as a reflection of a frustrated immune response unable to control HIV,[80] may even accelerate the disease.[81] There are, however some studies on the effects of anti-TNF-α therapy on the course of HIV infection which have been reviewed.[82] Case reports and small series of IBD patients or patients with rheumatic diseases have indicated that neither infliximab nor etanercept worsened in general HIV infection.[78,83–86] A unique report described a reduction in HIV virus load after infliximab infusion in a non HAART-treated HIV-patient.[87] A study investigated the effect of a four week therapy with etanercept (25 mg twice weekly) in 16 untreated HIV patients with smear positive tuberculosis and CD4+ cells $>$200/mm3. The clinical response to antituberculous chemotherapy was at equivalent or superior to a historical treatment group,[88] although it is difficult to recommend such a high-risk strategy. These data suggest that anti-TNF therapy may be given to IBD patients with coexisting HIV infection and might not have the detrimental effects on HIV infection.[78,83,84] Therefore, HIV patients may be treated with immunosuppressants if necessary by the clinical pattern of IBD but they should be carefully and closely monitored.

3.3.3. Preventive measures

General measures to prevent HIV infection are appropriate. These include educational initiatives to avoid sexual transmission by using condoms and avoiding shared needles in intravenous drug users. Post-exposure prophylaxis is appropriate for health professionals exposed to contaminated injection needles or blood from HIV-positive individuals. Local guidelines are likely to be available and specialist advice is appropriate.

3.3.4. Diagnostic approach, screening and treatment of the underlying infection

3.3.4.1. Diagnostic approach and screening. All IBD patients undergoing immunomodulator or biological therapy are best tested for HIV infection (through HIV p24 antigen and antibody testing, with PCR only if acute infection is suspected) to rule out unknown infection, because of the potential consequence of such therapy in HIV patients. It is reasonable to take the risk of acquiring HIV into account. The diagnosis of inflammatory bowel disease in HIV-infected patients should be reviewed and treatment managed in conjunction with appropriate specialists.

3.3.4.2. Treatment of the infection. Due to the scarce clinical data on the effect of immune reconstitution following treatment with HAART on the course of concomitant HIV and IBD, no recommendations are available.[82] It is reasonable to

assume that HAART will control viral replication and induce immune reconstitution, so that HIV-infected IBD patients will have fewer infectious complications from immunosuppressive IBD therapy than if they did not receive HAART. The susceptibility to infection of IBD patients suffering from HIV greatly depends on the success of HAART. When the CD4+ count is N350/μl the risk may be little different to those without HIV, but CD4 count less than 200 increases the risk. Aboulafia et al. reports the death of a HIV-infected man treated with etanercept for psoriasis of bacterial infection. He was receiving HAART but his CD4 count was 56/μl.[89] However, potential interactions between immunomodulators and HAART, apart from possible modification of the success of HAART, are largely unknown. There may be cumulative, additive, synergistic, or antagonistic effects of the different drugs in terms of pharmacokinetics, pharmacodynamics, or side effects (www.hiv-druginteractions.org).

3.3.5. Infection occurring during immunomodulator therapy

Primary HIV infection can occur during immunomodulator therapy but its occurrence should be rare. One case-report described a woman with Crohn's disease who acquired primary HIV infection during therapy with azathioprine, with HAART prescribed at this moment for one year.[87] From a practical point of view, symptomatic HIV infection should be treated according to discussion with appropriate specialists. Interruption of immunomodulator or biological therapy should be considered if there is no response to HAART (either by clinical improvement, or increase in CD4+ count).

4. Herpesviruses (HSV, VZV, EBV, CMV), human papilloma virus, and influenza virus

4.1. Cytomegalovirus (CMV) infection

ECCO statement OI 4A

Screening for CMV infection is not necessary before starting immunomodulator therapy [EL4]. In patients with acute steroid-resistant colitis, CMV should be excluded, preferably by tissue PCR or immunohistochemistry, before increasing immunomodulator therapy [EL3]. In case of severe steroid-resistant colitis with CMV detected in the mucosa during immunomodulator therapy, antiviral therapy should be initiated and discontinuation of immunomodulators considered until colitis symptoms improve [EL5]. In case of systemic CMV disease, immunomodulator therapy must be discontinued [EL2]

4.1.1. Background

See supplementary material.

4.1.2. Impact of immunomodulator therapy on natural history of the disease

Immunomodulator therapy is often associated with subclinical reactivation of latent CMV infection.[106] This reactivation is usually asymptomatic, or characterised by a mild, self-limited course. Serious tissue damage is very rare.[90,107] It is appropriate to draw a distinction between CMV infection (detectable by serology or viral DNA), and CMV disease (such as colitis, causing end-organ damage). Matsuoka et al. have demonstrated that CMV is frequently reactivated in patients with UC treated with steroids or 6-mercatopurine, but disappears without antiviral therapy.[108] In their series, CMVantigen concentrations were low in all patients and none had clinical symptoms or CMV detected in biopsy specimens. These data agree with previous studies showing that subclinical reactivation of CMV during immunomodulator or biological therapy is common, but nearly always self-limited even if therapy is continued.[109–113] Consequently, with the exception of severe infection (see below), immunomodulator treatment may be continued during CMV reactivation.

4.1.3. Preventive measures

There is no CMV vaccine available. Although different nucleoside analogues are effective therapy for severe CMV infection, the potential for adverse events does not justify standard chemoprophylaxis.[90,91,106]

4.1.4. Diagnostic approach, screening and treatment of the underlying infection

4.1.4.1. Diagnostic approach and screening. Only a minority of CMV infections lead to clinical disease, so screening for subclinical CMV infection in IBD patients is not indicated unless the patients are steroid resistant.

Different techniques for the diagnosis of CMV infection are available. The high seroprevalence in the adult population means that serology is of limited value for the diagnosis of active infection, but detection of CMV-specific antibodies can be used to diagnose recent infection (CMV IgM, change in IgG concentration, or IgG avidity). This identifies patients at risk from CMV reactivation (CMV IgG positive).[91] Conventional viral culture and the faster shell vial culture are highly specific, but have disadvantages including long incubation, lack of viral quantification, false-negative results if cell culture inoculation is delayed, and lower sensitivity compared to antigenaemia assays or PCR. CMV antigenaemia assays are only semiquantitative, but act as an indirect marker of disseminated infection. They are sufficiently rapid to monitor infection and antiviral treatment in immunocompromised patients, if measurement of viral load by PCR is not readily available.[91,113] Histopathology combined with immunohistochemistry (IHC, using monoclonal antibodies against CMV immediate early antigen) are highly specific and sensitive for verifying CMV infection in tissue or biopsies. The most commonly used technique for diagnosis of CMV infection and disease is detection of CMV DNA through PCR in tissue biopsies and in the blood. The advantages of PCR are rapid results, high sensitivity, the potential for qualitative and quantitative testing, detection in a wide range of samples (whole blood, buffy coat specimens, bronchoalveolar lavage (BAL) fluid and stool) and applicability in neutropenic patients.[91,94,113] In patients with severe colitis, CMV has been reported in colonic tissue in 21–34% and in 33–36% of steroidrefractory colitis.[104] The viral load (>250copies/mg) has been shown to be a predictor of steroid resistant disease.[114]

4.1.4.2. Treatment of the infection. Ganciclovir (for 2–3 weeks) is the therapy of choice for CMV infections.

After 3–5 days, a switch to oral valganciclovir for the rest of the 2- to 3-week course may be considered if available, depending on the clinical course and local specialist advice.[97,98,114] In cases of ganciclovir resistance or intolerance (e.g. myelotoxicity), foscarnet (for 2–3 weeks) is an alternative.[105,106]

4.1.5. Infection occurring during immunomodulator therapy
Subclinical or mildly symptomatic reactivation does not require treatment or interruption of immunomodulator therapy and usually passes unrecognised.[107] Systemic CMV reactivation causing meningo-encephalitis, pneumonitis, hepatitis, oesophagitis, or colitis, is rare, but associated with a poor outcome.[94,96,98] Prompt antiviral treatment with ganciclovir or other agents and discontinuation of immunosuppressive agents is associated with clinical improvement and decreased mortality,[94–98] so are recommended.

4.2. Herpes simplex virus (HSV)

ECCO Statement OI 4B

Screening for HSV infection is not necessary prior to initiation of immunomodulator therapy [EL2]. HSV infection is not a contraindication to immunomodulator therapy [EL2]. The need for oral suppressive antiviral therapy should be considered in patients with recurrent oral or genital HSV infection at commencement, or arising during immunomodulator therapy [EL2]. If there is a clinical suspicion, HSV colitis is best excluded by immunohistochemistry or tissue PCR as a cause of immunomodulatory refractory IBD before increasing immunomodulator therapy [EL4]. In the event of severe HSV disease during immunomodulator therapy, antiviral therapy should be initiated and immunomodulators discontinued until symptoms improve [EL4]

4.2.1. Background
See supplementary material.

4.2.2. Impact of immunomodulator therapy on natural history of the disease
Primary or recurrent oral and genital herpes may be more frequent, severe and extensive in immunocompromised patients.[115,116] In a prospective study, IBD patients receiving azathioprine therapy self-reported significantly more skin or genital herpetic flares compared with patients on mesalazine.[118]Reactivation may cause severe localised systemic infections with significant morbidity and mortality including encephalitis,[119–121] meningitis,[122] pneumonia,[123] oesophagitis,[124] and colitis.[125–129] HSV has increased potential for dissemination in immunocompromised individuals.[130,131] Fulminant herpes simplex hepatitis may be the initial manifestation of disseminated HSV disease.[132,133] This rare but devastating complication of HSV is more common even in marginally immunocompromised individuals.[134]

4.2.3. Preventive measures
There is no vaccine available for HSV.[135,136] Patients should be asked if they have a history of orolabial, genital or ophthalmic HSV infection, prior to immunosuppressive therapy.[137] Specialist review and advice should be sought for patients with prior HSV keratitis. Routine prophylaxis to suppress virus replication should be considered for patients with recurrent attacks and/or who are already taking intermittent suppressive antiviral therapy. Aciclovir 400 mg twice daily, valaciclovir 500 mg daily, or famciclovir 250 mg twice daily are suitable as prophylaxis[138]

4.2.4. Diagnostic approach, screening and treatment of the underlying infection

4.2.4.1. Diagnostic approach and screening. Detection of HSV antibodies indicates prior exposure and ongoing latent infection with HSV, but screening is not required. Serological responses appear late and are unsuitable for diagnosis. Patients with ophthalmic or genital symptoms should be referred for specialist assessment. See VZV section for laboratory diagnosis of HSV in skin lesions.

4.2.4.2. Treatment of the infection. Aciclovir or the oral prodrugs valaciclovir or famciclovir in therapeutic doses for HSV.

4.2.5. Infection occurring during immunomodulator therapy
HSV reactivation often runs a mild, self-limited course, not requiring discontinuation of immunomodulators or systemic antiviral therapy.[139] Nevertheless, immunomodulators should not be initiated during active HSV infection, since it may be exacerbated or even disseminate during immunosuppressive therapy.[93] Caution for possible HSV dissemination is warranted when considering azathioprine in a patient with active orofacial or genital HSV. Although extremely rare, HSV may cause hepatitis,[132,133] encephalitis,[121] colitis,[125–128] or pneumonitis[123] during immunosuppressive therapy for IBD. Antiviral therapy with intravenous aciclovir or foscarnet and discontinuation of immunosuppressants are appropriate.[125,126,128] HSV encephalitis and other severe or life-threatening manifestations of HSV warrant careful multidisciplinary management. Whether or when anti-TNF treatment can be reinstituted and the need for valaciclovir/aciclovir prophylaxis warrants careful consideration on a case-by case basis.[119] HSV colitis is very rare even in patients with IBD, but it might cause or mimic an acute relapse.[125–128] The risk of colectomy is high.[126]

4.3. Varicella zoster virus (VZV)

ECCO Statement OI 4C

At diagnosis of IBD, patients should be screened by history for susceptibility to primary VZV infection. Those without a clear history of chickenpox, shingles or receipt of two doses of varicella vaccine should be tested for VZV IgG [EL2]. Where possible, seronegative patients should complete the two dose course of varicella vaccine at least 3 weeks prior to commencement of immunomodulator therapy [EL5]. Subsequent immunisation can only be administered after a 3–6 month cessation of all immunosuppressive therapy [EL4]. Seronegative patients should receive timely post-exposure prophylaxis [EL4]

ECCO Statement OI 4D

Immunomodulator therapy should not be commenced during active infection with chickenpox or herpes zoster [EL4]. In the event of VZV infection during immunomodulator therapy, antiviral treatment should be started promptly [EL1] and immunomodulator therapy discontinued in severe cases if possible [EL5]. Immunomodulator therapy can be reintroduced after all vesicles have crusted over and fever has resolved [EL5]

4.3.1. Background

See supplementary material.

4.3.2. Impact of immunomodulator therapy on the natural history of the disease

Chickenpox is more often severe or life threatening in immunocompromised patients, causing pneumonia, hepatitis, encephalitis or haemorrhagic disorders (thrombocytopenia or disseminated intravascular coagulopathy).[147,148] In a review of VZV in IBD, five of 20 cases of varicella proved fatal.[149] IBD patients, especially those on immunomodulators, had an increased risk of zoster: 1.21 for UC and 1.61 CD in a case-controlled study.[150] Shingles is also more severe with an increased risk of post herpetic neuralgia.[140,142] Among 32 reported IBD patients with shingles, 25 were receiving thiopurines, 14 as monotherapy. Seven patients had evidence of visceral dissemination, including five with CNS disease.[149]

4.3.3. Preventive measures

In countries with a policy of routine childhood vaccination, the live virus varicella vaccine is given at 12–18 months with a booster at 4–6 years. Two doses of varicella vaccine provide protection from severe chickenpox.[140,148,151]

At diagnosis of IBD, unvaccinated adults and children should be screened by history of chicken pox (or shingles) for susceptibility to primary infection.[124] If the history is uncertain or negative, or the patient grew up in a tropical or subtropical climate, they should be tested for varicella zoster virus IgG.[124,149,152] It is important to avoid testing a sample which may contain VZV IgG obtained passively for example by blood transfusion.

Where possible, seronegative immunocompetent patients with IBD should receive two doses of varicella vaccine, a month or more apart, completing the course at least 3 weeks before any immunomodulators are started.[151,153,154] Subsequent immunisation should only be administered 3–6 months following cessation of all immunosuppressive therapy, including high dose steroid monotherapy.[155,156] Adults receiving 40 mg of prednisolone (or equivalent) daily for a week or more are deemed to be on high dose steroids, as are children receiving prednisolone, orally or rectally, at 2 mg/kg/day for at least one week, or 1 mg/kg/day for one month.[156]

4.3.3.1. Post-exposure prophylaxis. Varicella zoster immune globulin (VZIG) should be administered within 10 days when an unimmunised, seronegative, high-risk patient with IBD (immunosuppression, pregnancy) has had significant exposure to chicken pox, disseminated zoster, or shingles on exposed skin.[151,153,157,158] After VZIG, patients should be observed for 28 days, and treated in the event of varicella.[151,153]

4.3.3.2. Zoster vaccine. 14 times more potent than the matching live varicella vaccine, provides significant protection from both zoster and post herpetic neuralgia.[159] It is licensed in many countries and a single dose is routinely recommended for immunocompetent individuals of over 60 years.[160] Immunisation of IBD patients receiving immunomodulators would require significant immunomodulator-free periods before and after administration as outlined for varicella vaccination. According to US CDC Guidelines however, therapy with low-doses of methotrexate ($\leq$0.4 mg/kg/week) azathioprine ($\leq$3.0 mg/kg/day) or 6-mercaptopurine ($\leq$1.5 mg/kg/day) are not considered sufficiently immunosuppressive to create vaccine safety concerns and are not regarded as contraindications for administration of zoster vaccine.[160] Recent data from Zhang et al. indicates that zoster vaccine may be safe in patients treated with anti-TNF.[161] Still, the efficacy and safety of this vaccination strategy is not clear in IBD patients treated with immunomodulators so physicians should remain cautious and further data are needed.

4.3.4. Diagnostic approach, screening and treatment of the underlying infection

4.3.4.1. Diagnostic approach and screening. Serology is not useful for diagnosis of chickenpox or shingles. VZV can readily be detected in blister material scraped or swabbed from a disrupted skin lesion. The choice of test depends on the available technology. Nucleic acid amplification technology tests are specific and sensitive (both approaching 100%), and can detect VZV DNA in crusted lesions, although deemed no longer infectious.[162] Older technologies, including rapid antigen detection, Tzanck smear (for multinucleate giant cells), and electron microscopy, are more reliant on the quality and timing of the sample, and the skill of the microscopist. Positive Tzanck or electron microscopy tests do not differentiate between VZV and HSV.[162] Commercial tests for VZV IgG have suboptimal sensitivity but work is underway to improve the reliability and to define antibody cut-off levels for susceptibility.[163] Available tests are not optimised to detect antibody to the vaccine virus.[163]

4.3.4.2. Treatment of the infection. Suspected varicella or zoster warrants prompt action in IBD, and therapy should be initiated pending test results. VZV requires higher treatment doses than HSV, and the newer agents valaciclovir or famciclovir, with higher oral bioavailability, are preferable to acyclovir when oral therapy is appropriate.[140,141]

4.3.5. Infection occurring during immunomodulator therapy

Immunomodulators should not be initiated during chickenpox or shingles. Patients should be carefully assessed, and treated promptly with specialist advice.[141] It may be advisable to stop immunomodulator therapy until clinical resolution.[149,164–170]

4.4. Epstein–Barr virus (EBV)

ECCO Statement OI 4E

Screening for EBV infection before initiation of immunomodulator therapy should be considered [EL5]. In severe primary clinical EBV infection during immunomodulator therapy, antiviral therapy may be considered and immunomodulator therapy discontinued [EL5]. In the event of EBV-driven lymphoproliferative disease during immunomodulator therapy, the patient should be managed in conjunction with appropriate specialists. Immunomodulators should be stopped.

4.4.1. Background

See supplementary material.

4.4.2. Impact of immunomodulator therapy on the natural history of the disease

In the normal host, EBV infected B-cells persist in the circulation with minimal expression of latency genes, thereby avoiding destruction by EBV-specific cytotoxic T-lymphocytes.[172] When T-cell immunosurveillance is impaired, *eg* post-transplant, enhanced EBV latent gene expression drives the proliferation of EBV-infected B-cells, and the attendant risk of post-transplant lymphoproliferation/lymphoma (PTLD).[172,173] Primary EBV infection in the first post-transplant year is associated with a much increased risk of PTLD.[171,174,175]EBV IgG testing pre-transplant identifies susceptible patients and coupled with post-transplant EBV DNA surveillance facilitates early recognition of primary infection and prompt reduction of immunosuppression.[174]

In recent years accumulated data has shown an increased, albeit small, risk of lymphoma among IBD patients, especially those on thiopurines.[176–179] In the Cesame cohort of almost 20,000 patients, current thiopurine therapy had a hazard ratio of 5.28 for development of lymphoproliferative disorder.[176] The overall risk remains small, estimated to result in one additional lymphoma for every 300–1400 years of thiopurine treatment, but EBV seems to be implicated, with a propensity for intestinal presentation.[176–180] In Cesame cohort patients on thiopurines, 12 of the 15 lymphomas were PTLD-like (and usually EBV-associated), versus 1 of 8 lymphomas in patients not on thiopurine therapy. Primary EBV infection may pose a particular threat: among 6 patients under 50 years in the thiopurine group, two males had fatal infectious mononucleosis associated lymphoproliferative disorders.[176] Two additional cases of fatal infectious mononucleosis have been reported in CD patients on azathioprine.[181,182]

4.4.3. Preventive measures

No EBV vaccine is available. Prophylaxis with aciclovir or ganciclovir after renal transplantation has been reported to reduce the risk of lymphoma in renal transplant recipients,[174] but the risk of lymphoma in IBD is too low to justify this approach.

EBV IgG screening should be considered before initiation of immunomodulator therapy.[176,183] Anti-TNF monotherapy could then be used in preference to thiopurines in EBV seronegative patients at the clinician's discretion.

4.4.4. Diagnostic approach, screening and treatment of the underlying infection

4.4.4.1. Diagnostic approach and screening. The Paul–Bunnell and monospot tests are suboptimal for diagnosis. Primary EBV infection is diagnosed by the detection IgM and IgG directed against the EBV viral capsid antigen (VCA) with negative EBNA1 IgG. EBNA1 IgG usually appears weeks or months later.[184] Post-transplant EBV viral load monitoring has a high sensitivity for current or future EBV-associated PTLD in high risk HSCT and seronegative solid organ transplant recipients, but poor specificity.[185,186] The limited IBD data shows negligible or self-limited increases in sequential EBV viral load measurements after introduction of immunomodulators, without associated EBV-associated disease.[110,187] Biopsy diagnosis and classification by a specialist haematopathologist is required to differentiate infectious mononucleosis from lymphoproliferative disease, non-Hodgkin's lymphoma and Hodgkin's disease. Analysis must include EBER *in situ* hybridisation to detect the presence of EBV.[188] Immunohistochemistry for EBV is not an adequate substitute as viral proteins *e.g.* LMP-1 are often not expressed.[188,189]

4.4.4.2. Treatment of the infection. Aciclovir therapy does not ameliorate the course of infectious mononucleosis in otherwise healthy individuals.[190] Steroid therapy may be indicated for airway obstruction. Anti-viral agents have no proven role in the treatment of established PTLD, reflecting the limited productive viral infection.[175]

4.4.5. Infection occurring during immunomodulator therapy

Possible primary EBV infection warrants careful clinical assessment, with full blood count and blood film, liver function tests and EBV serology. Immunomodulator therapy should be reduced or discontinued if possible. In severe primary EBV infection, antiviral therapy with ganciclovir or foscarnet may be considered, despite the lack of supporting evidence.[175,190] These agents are more potent than aciclovir for replicative EBV infection, but are more toxic.

Specialist advice should be sought for investigation and management of suspected lymphoproliferative disease/lymphoma. Discontinuation of immunosuppressive therapy may result in spontaneous regression of EBV-associated lymphoproliferative disease.[175,191,192] In the absence of spontaneous regression, or progression after interruption of immunomodulators, rituximab is the next line of therapy for CD20 positive B-cell EBV-associated lymphoproliferative disease. Chemotherapy may also be required.

4.5. Human papilloma virus (HPV)

ECCO Statement OI 4F

Regular gynaecologic screening for cervical cancer is strongly recommended for women with IBD, especially if treated with immunomodulators [EL2]. In patients with extensive cutaneous warts and/or condylomata, discontinuation of immunomodulator therapy should be considered [EL5]. Routine prophylactic HPV vaccination is recommended for females and males according to national guidelines [EL2]. Current or past infection with HPV is not a contraindication for immunomodulator therapy [EL2]

4.5.1. Background

See supplementary material.

4.5.2. Impact of immunomodulator therapy on natural history on the disease

It is unclear how immunomodulators can modify the course of the disease, but there are reports of viral reactivation in immunocompromised patients[198,199] Several studies in women undergoing organ transplantation demonstrated an increased risk of cervical dysplasia, HPV infection and persistence.[200–203] Moreover, studies in women affected by IBD also observed that HPV-associated Pap-smears abnormalities were more frequent.[204,205] Therefore, immunosuppressive agents including TNF blockers could increase the risk of persistent HPV infection and ultimately cervical cancer.

4.5.3. Preventive measures

Since 2006 a prophylactic quadrivalent vaccine (Gardasil ®, Silgard®) using L1 virus-like particles (VLP) of HPV-6, -11, -16 and -18 is available in Europe. In 2007, a bivalent vaccine (Cervarix®) containing L1 VLPs of HPV-16 and -18 was approved in Europe. Both vaccines are highly immunogenic, safe and offer high protection (95–100%) against HPV infection in immunocompetent patients.[206,207]Depending on local guidelines, routine HPV vaccination is recommended for females aged 11–14 years before onset of sexual activity. In the event of missed or delayed vaccination, local guidelines variably recommend HPV vaccination to females younger than 26 years old, in some cases depending on beginning of sexual activity.[208] The quadrivalent vaccine is now recommended in USA for males too aged 11–12 years old, with catch-up vaccination for those younger than 26 years old[208] HPV immunisation uses a non-live agent, so it can be administered to immunocompromised IBD patients. American guidelines propose to recommend it to immunocompromised persons through age 26 years (males and females) who did not get any or all doses when they were younger.[208] A recent study investigated 37 females with IBD, 51% being treated with anti-TNF agents and 49% receiving immunosuppressants.[209] Interestingly, in this small study 3 doses of the HPV vaccine Gardasil® were highly immunogenic and without significant vaccine-associated side effects.

4.5.4. Diagnostic approach, screening and treatment of the underlying infection

Measurement of serum antibodies (IgG and IgA) to type-specific virus-like particles (VLPs) or capsids is a useful marker of prevalent or persistent HPV exposure and reflects infection whatever the anatomical site. Such antibodies are inadequate for diagnosis of HPV infection, because not all patients seroconvert after HPV exposure and HPV antibodies can take a year or more to appear.[210,211] Identification of HPV DNA via PCR is specific for diagnosis of a HPV infection, but since HPV infection is transient and usually clears within 2 years, it is limited to the detection of current infection.[212] Cervical smear testing in immunocompromised women is recommended as for the general population.[213,214] A practical point is to ask female patients on immunomodulators whether they have had a cervical smear. HPV screening is not recommended for men in the general population, because there is currently no evidence that screening or treatment reduces the risk of progression to (anal) cancer in this group.[193]

4.5.4.1. Treatment of the infection. No antiviral agents for eradicating or treating of HPV infections are known. Treatment options for HPV-associated carcinoma include surgery, chemo- and radiotherapy.[213,215]

4.5.5. Infection occurring during immunomodulator therapy

Few studies describe a higher prevalence of abnormal cervical ('Pap') smears associated with HPV-16 and -18 in women with IBD compared to the general population. The risk of an abnormal smear associated with HPV-16 and -18 has also been reported to increase in patients on immunomodulator therapy.[204,205,216] On the contrary, a large retrospective case–control study in Scotland did not find any difference in rates of abnormal smears between IBD women and controls.[217] In all studies, confounding factors like smoking and sexual activity are rarely explored. Even if data still remain conflicting, women with IBD and especially those on immunomodulators are best advised to have regularly screening as high risk patients according to local or ACOG guidelines.[218] The American Cancer Society recently recommended that women who are immunocompromised should be tested twice during the first year of diagnosis and annually thereafter.[219] They may be considered candidates for HPV vaccine regardless of their sexual history.[204,205] Nevertheless, infection with HPV is no contraindication to immunosuppression. Anal carcinoma and squamous cell carcinoma (SCC) in particular are considered rare complications of IBD (perhaps more common in those with chronic fistulizing Crohn's disease) and may be associated with infection with carcinogenic types of HPV.[215]

There are reports of an increased frequency of anogenital warts in immunocompromised patients.[220] Discontinuation of immunomodulators may be helpful in patients with extensive anogenital warts. Infection with HPV while on immunomodulators does not otherwise present a clinical problem, although there are occasional cases of disseminated cutaneous warts in patients who have been on azathioprine for years. Treatment is best conducted with a dermatologist, but the risk of exacerbating the underlying IBD by withdrawing azathioprine has to be considered and discussed with the patient. Extensive

genital warts in psoriasis patients undergoing anti-TNF therapy have been reported in small case series.[221,222]

4.6. Influenza virus

ECCO Statement OI 4G

Patients on immunomodulator therapy are considered to carry an enhanced risk for the development of severe influenza infection [EL5]. Annual vaccination with trivalent inactivated influenza vaccine is an effective strategy to prevent influenza [EL1]. The live attenuated vaccine is not recommended. Vaccination does not appear to have an impact on the activity of inflammatory bowel disease [EL3]. Routine influenza vaccination of patients on immunomodulators is recommended in accordance with national guidelines [EL5]. Seroconversion after influenza vaccine is reduced in patients receiving immunomodulator therapy, particularly in those on combination therapy [EL3]

ECCO Statement OI 4H

Immunosuppressed patients with a laboratory diagnosis of influenza should receive prompt treatment early in the course of illness, whether or not an influenza epidemic has been declared. Empiric treatment should be given on clinical grounds during an epidemic in accordance with national guidelines [EL5]

4.6.1. Background

See supplementary material.

4.6.2. Impact of immunomodulator therapy on natural history on the disease

Limited data exist on the epidemiology of influenza infection in patients with IBD. While the incidence of influenza does not appear greater in IBD patients receiving immunomodulators,[225] immunosuppression is generally considered to enhance the risk of severe/complicated influenza infection.[226]

4.6.3. Preventive measures

4.6.3.1. Vaccination. Annual vaccination is the most effective method for preventing influenza virus infection and is therefore recommended for patients on immunomodulators in guidelines from the American Center for Disease Control (CDC).[223] Two types of vaccines are available. Live attenuated influenza vaccine (LAIV) should only be used for healthy persons age 5–49 years and is not recommended for patients on immunomodulators. In contrast, the trivalent inactivated influenza vaccine (TIV) may be used for any person older than 6 months, including those on immunomodulators.[223] IBD patients on immunomodulators are considered to be at risk and annual TIV vaccination has been recommended.[227] However, compliance with these recommendations remains poor[228,229] and definitive proof of benefit is circumstantial.[230] There is emerging data to suggest that influenza vaccination may be less effective in patients with IBD receiving immunosuppressants, particularly those receiving combination therapy.[231–233] The use of anti-TNF monotherapy may also reduce response to vaccination.[234,235] However, the immune response remains sufficient to warrant annual influenza vaccination. Influenza vaccination appears safe in patients with IBD and is not associated with a risk of flare of disease.[236]

4.6.3.2. Chemoprophylaxis. Both oseltamivir and zanamivir can decrease the risk of symptomatic infection, when given in the early phase after close contact with a patient with laboratory confirmed influenza.[237,238] Recommendations relating to the use of post-exposure prophylaxis for household contacts show significant country to country variation.[239] CDC guidelines suggest chemoprophylaxis be considered if an individual at high risk or influenza complications, such as an IBD patient who is immunosuppressed, has a household member or close contact with a person with influenza.[240]

4.6.4. Diagnostic approach, screening and treatment of the underlying infection

4.6.4.1. Diagnostic approach and screening. Influenza is characterised by the sudden onset of constitutional and respiratory symptoms (myalgia, headache, malaise, cough, core throat and rhinitis), typically with fever. In most cases, the diagnosis is based upon symptoms and knowledge of the local active prevalence of influenza infection. Diagnostic tests for influenza can aid clinical judgment and include viral culture, serology, rapid antigen testing, reverse transcriptase–polymerase chain reaction (RT-PCR), and immunofluorescence assays. Influenza antiviral agents should only be used for treatment of acute clinical symptoms compatible with influenza at a time when public health agencies report that influenza is prevalent in the community, or when influenza is specifically diagnosed by rapid antigen tests.[240]

4.6.4.2. Treatment of influenza infection. Four antiviral agents with activity against influenza virus are available: amantadine, rimantadine, zanamivir, and oseltamivir. Resistance of influenza virus to amantadine and rimantadine is appreciable, so these drugs are not currently recommended.[240] When zanamivir or oseltamivir are started within 48 h of the onset of symptoms, a reduction in fever and cough from 1.5 days to 3 days has been demonstrated. Significant differences compared to placebo were found only in those treated within 36 h of onset for oseltamivir and within 30 h of onset for zanamivir.[241,242] Country specific European guidelines recommend antiviral therapy for patients at high risk of complications, except Germany where there is a strong recommendation to treat all patients.[239] Zanamivir solution for intravenous injection or nebulisation has been proposed in cases of complicated influenza or oseltamivir resistance.[240]

4.6.5. Infection occurring during immunomodulator therapy

CDC guidelines recommend early use of antiviral therapy in suspected or confirmed influenza infection in all

immunocompromised patients, in order to reduce risk of influenza-related complications.[240]

5. Parasitic and fungal infection

ECCO Statement OI 5A

The risk of fungal infection in inflammatory bowel disease seems to be low. Systemic infections are exceptional, but mortality is high [EL4]. No vaccines exist for prevention of fungal infection. Primary chemoprophylaxis is currently not indicated. Secondary chemoprophylaxis should be discussed with an appropriate specialist [EL5]

5.1. Background and impact of immunomodulator therapy on natural history of the disease

See supplementary material.

5.2. Preventives measures and screening

5.2.1. Immunisation and chemoprophylaxis for *P. jiroveci*

ECCO Statement OI 5B

No vaccines are available for prevention of *P. jiroveci* pneumonia. For patients on triple immunomodulators with one of these being either a calcineurin inhibitor or anti-TNF therapy, standard prophylaxis with co-trimoxazole is recommended if tolerated [EL4]. For those on double immunomodulators, prophylactic co-trimoxazole should be considered especially if one of these is a calcineurin inhibitor [EL 4]

There is no consistency in the approach to prophylaxis against *P. jiroveci* in patients with IBD treated with immunomodulators, despite some suggested guidelines.[249,250] A meta-analysis showed a 91% reduction of occurrence of *P. jiroveci* when chemoprophylaxis with cotrimoxazole was administered in patients with haemotological cancers or transplants.[251] Patients with HIV disease and a CD4+ count below 200/mL were at lower risk with infections with *P. jiroveci* when maintained on cotrimoxazole.[252] It is rare for patients to acquire P. jiroveci infection when the CD4+ count is above 200/mL. There are multiple regimen for primary chemoprophylaxis: Trimethoprim–sulphamethoxazole (TMP-SMZ) is the prophylactic agent of choice with one-strength tablet daily (80–400 mg) or half-dose daily of a double strength tablet (160–800 mg) or a double-strength tablet three times per week.

5.2.2. Immunisation and chemoprophylaxis for parasitic and fungal infections except *P. jiroveci*

ECCO Statement OI 5C

Screening for parasitic or fungal infection prior to immunomodulator therapy is generally considered unnecessary. Specialist advice should be sought for patients that have lived or travelled in endemic areas [EL5]

In contrast to transplant patients, there is no evidence to support a general policy of screening for parasitic or fungal infections prior to initiating immunomodulator or biological therapy. Patients returning from endemic areas or a past history of parasitic or fungal infections represent special cases. In the case of *S. stercoralis*, in particular, screening of patients with risk factors could be performed, although no method is ideal. Positive serology in a patient with a compatible clinical history preparing to undergo steroid therapy may be considered sufficient grounds for therapy (with ivermectin ideally or with albendazol). Therapy could be also considered in these patients even without a serology. Specialist advice should be sought.

Secondary prophylaxis guidelines for Candida and Aspergillus are available for transplant, cancer and ICU patients with neutropenia, however IBD patients under immunosuppression are not considered.[253,254] Nevertheless, secondary prophylaxis may be necessary in case of ongoing immunosuppressive therapy but this should be discussed with appropriate specialists.[254]

Specialist advice is recommended on the approach and interpretation of diagnostic tests. The succinct details in Table 1 are intended as a general guide for non-specialists. *P. jiroveci* is now classified as an atypical fungus. Diagnosis is based on the identification of *P. jiroveci* in bronchopulmonary secretions obtained as induced sputum or BAL fluid. Serum 1,3-β-D-glycan assay may be helpful as a marker for the diagnosis of *P, jiroveci* pneumonia with a sensitivity of more than 90%.[255] *P. jiroveci* trophozoites and cysts can be identified by light microscopy and molecular techniques (high sensitivity and specificity). A positive PCR may be found in asymptomatic patient and should therefore be interpreted with caution whereas a negative PCR value virtually excludes the infection.

5.3. Treatment of the infection

Pulmonary involvement is a feature with most systemic infections and fungal or parasitic pneumonia are potentially life threatening. Systemic cryptococcosis can cause pneumonia, but more commonly causes meningitis, sometimes without meningism. Strongyloides hyperinfection with alveolar haemorrhage and disseminated disease is more frequently reported in patients receiving high doses of steroids or other immunomodulators. The diagnosis should be suspected in any patient with pneumonia from an endemic area. Eosinophilia is present in up to 70% of the patients, and should raise suspicion of infection with *S. stercoralis*,[256] however severe cases may not have eosinophilia. Early implementation of therapy (such as parenteral ivermectin for disseminated strongyloidiasis) can be life-saving.

Table 1 Summary of diagnostic approaches to parasitic and fungal infections.

Pathogen	Culture	Serology	Molecular	Other
Pneumocystis jiroveci	−	−	+/−	Direct visualization/cytology
Strongyloides stercoralis	−	+	−	Direct visualization/cytology
Toxoplasma gondii	−	+	(+/−)	Clinical context−radiology
Candida spp.	+	(+/−)	(+/−)	
Aspergillus spp.	+	+	−	Clinical context−radiology
Histoplasma capsulatum	+	+	(+/−)	Radiology + direct visualization(histology)/antigen detection
Cryptococcus neoformans	+	−	−	Cytology/antigen detection

General guidance for treatment of parasitic and fungal infection is shown in Table 2. In patients with parasitic or fungal infection, other than oral or vaginal candidiasis, immunomodulator therapy should be stopped if possible and standard therapy for the infection implemented. Common sense dictates that if an opportunistic infection arises as a consequence or in association with immunosuppression it is unwise to reintroduce such therapy in that patient unless all other options are considered. If a decision is made to reintroduce immunomodulator once the infection has responded to treatment, because there are no other options for controlling the IBD, then consideration should be given to secondary prophylaxis and specialist advice taken.

6. Mycobacterium tuberculosis infection

ECCO Statement OI 6A

Reactivation of latent TB in patients treated with anti-TNFs is increased and is more severe than in the background population [EL2]. Latent TB should be diagnosed by a combination of patient history, chest X-ray, tuberculin skin test and interferon-gamma release assays (IGRA) according to local prevalence and national recommendations. Screening should be considered at diagnosis and always performed prior to anti-TNF therapy [EL5]. IGRA are likely to complement the tuberculin skin test and are preferred in BCG-immunised individuals [EL1]

ECCO Statement OI 6B

Patients diagnosed with latent TB prior to anti-TNF should be treated with a complete therapeutic regimen for latent TB [EL1]. In other situations, specialist advice should be sought. Chemotherapy for latent TB may vary according to geographic area or the patient's epidemiological background [EL5]. When there is latent TB and active IBD, anti-TNF therapy should be delayed for at least 3 weeks after starting chemotherapy, except in cases of greater clinical urgency and with specialist advice [EL5]

ECCO Statement OI 6C

When active TB is diagnosed, anti TB-therapy must be started, and anti-TNF therapy must be stopped but can be resumed after two months if needed [EL4]

6.1. Background

See supplementary material.

6.2. Preventive measures

International guidelines recommend TB risk evaluation before anti-TNF therapy, based on epidemiological risk factors, physical examination, chest X-ray, and tuberculin skin test (TST) for latent TB, but there are local variations. A diagnosis of latent TB should be considered when there is a history of recent exposure to the disease and positive initial tuberculin skin test (TST) or positive booster TST or IGRA test and no radiological evidence of active TB. A positive Mantoux reaction for TST is defined by an induration diameter ≥ 5 mm. An abnormal chest radiograph suggestive of old TB (calcification >5 mm, pleural thickening, or linear opacities) should also be considered suggestive of latent TB even if other criteria are absent.[267–270]

It is important to acknowledge that skin testing is sensitive, but its specificity for predicting reactivation tuberculosis is poor; only about 5% of immunocompetent persons with a positive test will have progression from latent infection to disease in their lifetime.[271] Diagnosis of latent TB by TST may be in particular distorted by prior BCG (Bacillus Calmette–Guerin) vaccination, because vaccinated individuals may become positive reactors to purified protein derivate (PPD). This distortion is almost insignificant in adults above 30 years of age, irrespective of age at vaccination or re-vaccination. TST may also be false negative in patients on corticosteroids for >1 month, or thiopurines or methotrexate for >3 months. TST cannot adequately be interpreted if corticosteroids are not discontinued for >1 month and immunomodulators for >3 months. Consequently, a booster TST may be appropriate for patients on immunomodulators with a negative TST 1–2 weeks after the first test. A false negative TST may also occur during active IBD without immunosuppression. In clinical practice, booster TST diagnoses 8–14% additional cases of latent TB among rheumatologic or IBD patients.[272–276] Any TST ≥ 5 mm should be considered positive for latent TB. Two new

Table 2 General guidance for treating parasitic or fungal infections.

	Preferred regimen	Second-line	Duration
Pneumocystis jiroveci	Co-trimazole (trimethoprim + sulphamethoxazole)	Pentamidine	14–21 days
Strongyloides stercoralis	Ivermectin	Albendazole	2–3 days
Toxoplasma gondi	Sulphadiazine and pyrimethamine	Clindamycin plus pyrimethamine	21–28 days
Invasive *Candida albicans* [a]	Fluconazole	Caspofungin	At least 14 days
Invasive *Candida non-albicans* [b]	Fluconazole	Voriconazole	2 weeks
Aspergilus spp.	Voriconazole	Amphotericin B deoxycholate	Until resolution of symptoms
Histoplasma capsulatum	Amphotericin B liposomal then Itraconazole	Amphotericin B deoxycholate	2–3 months
Cryptococcus neoformans	Amphotericin B deoxycholate + 5 Flucytosine	Fluconazole	10 weeks of induction and consolidation treatment (2 weeks of Amphhotericin B deoxycholate + 5 Flucytosine followed by fluconazole 400–800 mg/day for 8 weeks)

[a] Invasive *Candida albicans* with history of Fluconazole use, fluconazole should not be the preferred regimen.
[b] in *C. glabrata* and *C. krusei* Voriconale or Echinocandin.

diagnostic tests for tuberculosis infection have come on the market and they belong to interferon-gamma release assays (IGRAs), namely QuantiFERON–TB Gold (QFT) and the T-SPOT. The two commercially available IGRAs both use purified antigens from M. tuberculosis to stimulate peripheral-blood lymphocytes to produce interferon-γ. The QFT test measures the amount of interferon-γ in the supernatant of a cell suspension, whereas the T-SPOT determines the number of cells producing interferon-γ with the use of an ELISpot assay. IGRAs are more likely to be positive in persons who have recently been infected with *M. tuberculosis*, a group at particularly high risk for disease progression.[277] Another potential advantage of the IGRAs is that there is no cross-reactivity with the tuberculosis vaccine. Therefore, IGRAs may be particularly valuable in evaluating tuberculosis-infection status in persons who have received BCG vaccination as younger than 10 years old. Nine studies encompassing 1309 patients with IBD were investigated in a recent meta-analysis. The pooled concordance between the TST and IGRAs (QTF and QTF in-Tube) was 85% and the concordance of the TST and TSPOT.TB was 72%. Positivity was significantly influenced by immunosuppression.[278] Therefore, screening prior to initiation of IST should be considered, particularly in those on anti-TNF.

6.3. Impact of preventive action and chemoprophylaxis

In a post-marketing surveillance of Infliximab among 5000 Japanese patients with rheumatoid arthritis, Takeuchi and co-workers confirmed that chemoprophylaxis decreased the number of cases with overt TB.[279,280] TB chemoprophylaxis regimens are based on isoniazid (INH) for 6–9 months.[267,272,280–282] Individuals on chronic steroid therapy, defined as the equivalent of greater than or equal to 15 mg/day prednisone for at least 1 month, should receive isoniazid prophylaxis if they have a positive TST.[283,284] Randomised trials have shown that treatment is highly effective, with approximately 90% protection provided by completion of a 9-month course of isoniazid and 60 to 80% protection provided by completion of a 6-month course.[257] Rifapentine and isoniazid administered once a week for 3 months, had a low rate of serious hepatotoxicity[285] open-label randomised non-inferiority trial comparing 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg) (combination-therapy group) with 9 months of self-administered daily isoniazid (300 mg) (isoniazid-only group) in subjects at high risk for tuberculosis was as effective as 9 months of isoniazid alone in preventing tuberculosis.[286] Although this association was not yet tested on immunosuppressed patients.

Isoniazid-related hepatotoxicity occurs in approximately 0.15% of patients. It may occasionally be severe and life-threatening. The risk of liver damage with isoniazid is unrelated to the dose or blood concentration. An increased risk of isoniazid-related hepatotoxicity in patients with rheumatologic disease on concomitant methotrexate or sulphasalazine has been reported, but the association has not been established in IBD. Some authors advise monitoring liver function at intervals, with cessation or alteration of therapy if the transaminases exceed 3-fold associated with hepatitis symptoms or jaundice, or 5-fold in the absence of symptoms.[273,280,287–290]

No prospective or controlled data are available on the ideal timing of anti-TNF therapy once TB treatment has begun. It has been proposed that a pneumologist or infectious disease specialist should supervise TB therapy. It has also been suggested that anti-TNF treatment is either best delayed until completion of an antituberculosis treatment and should be avoided until at least 2 months after TB treatment has

begun.[291,292] There are no data assessing the impact of thiopurine therapy on the risk of TB in patients also receiving anti-TNF therapy. This suggests that thiopurines may be continued during treatment of TB, although studies are warranted.

7. Bacterial infection

7.1. Streptococcus pneumonia infection

ECCO Statement OI 7A

Patients with IBD on immunomodulators are considered to be at risk for pneumococcal infections [EL4]

ECCO Statement OI 7B

Pneumococcal vaccination should be given shortly before initiation of immunomodulators [EL5]. Immunity to *S. pneumoniae* after polysaccharide vaccination is altered by immunosuppression [EL2]

ECCO Statement OI 7C

Immunomodulator therapy should be temporarily withheld until the resolution of active infection. Treatment of pneumonia in patients on immunomodulators must always cover *S. pneumoniae* [EL5]

See supplementary material.

As pneumococcal capsular antigens induce serotype specific antibodies, both available vaccines (polysaccharide and polysaccharide conjugated) are able to produce serological response.[296] A 23-valent polysaccharide vaccine (PPV23) has been available for many years and a 7-valent conjugate vaccine (PCV7) has been licensed since 2001 in Europe. The 13-valent pneumococcal conjugate vaccine (PCV13) provides the same seroprotection as PCV7 and contains the 10 serotypes in PCV10 plus three additional pneumococcal serotypes: 3, 6A, and 19A[297] PCV10 was originally approved with a 3 + 1 dosing schedule but was recently approved for a 2 + 1 dosing schedule in Europe.[298] The PPV23 covers 80–90% of the serotypes responsible for invasive pneumococcal disease in Europe.[299] PPV23 vaccine is recommended in all older adults and in young children (more than 2 years of age) who have a high risk for pneumococcal disease.[297] Primary vaccination and revaccination every 5 years with PPV23 are well tolerated, induce robust, long-lasting immune responses and are cost effective. In children less than 2 years of age, the PCV7 seems to be effective in the prevention of invasive disease, severe pneumonia and serotype-specific otitis media.[300] PPV23 vaccine should ideally be administered before the start of immunomodulator therapy, since immunomodulators may reduce the antibody response. This has been shown in patients with rheumatic diseases[301–306] and IBD.[307,308] Therefore, the vaccine is best administered two weeks before the start of immunomodulators.[301] Advisory Committee on Immunization Practices (ACIP) recommends that adults aged $\geq$19 years with immunocompromising conditions and who have not previously received PCV13 or PPSV23 should receive a dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later. A second PPSV23 dose is recommended five years later. For those with previous vaccination with PPSV 23, a PCV 13 dose should be given $\geq$1 year after the last PPSV23[309]

The most frequent and severe manifestations of pneumococcal infection are pneumococcal pneumonia and pneumococcal meningitis (with or without pneumococcal bacteriemia). Antibiotic treatment of pneumonia in patients with IBD should always cover *S. pneumoniae*. Penicillin is the standard antibiotic for penicillin-susceptible pneumococcal pneumonia and meningitis, but local advice on resistance is appropriate,[310] especially since their immunosuppression may be associated with an increased risk of penicillin resistance. In most European countries, in particular in patients with meningitis, 3rd generation IV cephalosprins are recommended. In invasive pneumococcal infection, immunomodulator therapy is best temporarily withheld until resolution of the infection.[293,295,311]

7.2. *Legionella pneumophila* infection

ECCO Statement OI 7D

Patients with inflammatory bowel disease on immunomodulator therapy with pneumonia should be tested for *L. pneumophila* [EL4]. Immunomodulator therapy should temporarily be withheld until resolution of the active infection [EL5]

See supplementary material.

No vaccine is available and effective chemoprophylaxis has not been described. The key to diagnosis is appropriate sputum microbiological culture. Antigen detection in the urine (detects only *L. pneumophila*, serogroup 1; this accounts for 70 to 80% of cases) is easy done; direct fluorescent stain on respiratory specimens has sensibility ranged from 25 to 75%. Real-time PCR in throat swab specimens, bronchoalveolar lavage (BAL), urine, and serum has not shown to be more sensitive than culture, and therefore CDC does not recommend the routine use of genetic probes or PCR for the detection of Legionella in clinical samples[321] Serological testing is also available—a fourfold rise $\geq$128 in titer between the acute and convalescent titer is required for a definitive serologic diagnosis.[322]

Empirical treatment of severe community-acquired pneumonia should always cover *L. pneumophila* especially in the immunocompromised.[323,324] Macrolide or fluoroquinolones are the treatment of choice for *L. pneumophila*.[312,316] Immunomodulator therapy is best temporarily withheld until resolution of the active infection, however recurrent infection has been reported. Therefore, careful consideration is necessary about the benefit of continuing immunomodulators.[316]

7.3. Salmonella species infection

ECCO Statement OI 7E

Patients receiving immunomodulators are at risk of more severe infections with *Salmonella enteritidis* and *S. typhimurium* [EL4]. Prevention of Salmonella sp. infections consists of food hygiene and careful food choices (avoiding raw eggs, unpasteurised milk and insufficiently cooked or raw meat) [EL5]. Immunomodulators should be temporarily withheld until resolution of the active infection [EL5]

See supplementary material.

Salmonellosis is treated with antibiotics such as fluoroquinolones or third-generation cephalosporins, depending on the local susceptibility pattern. In rare cases of *S. typhimurium* osteomyelitis[333] or septic arthritis[334] combination of antibiotics and surgical treatment may be required. Immunomodulators should be temporarily withheld until resolution of the active infection as immunomodulator therapy is considered a high-risk predisposing condition for intestinal or systemic infections with *Salmonella* spp.[335]

7.4. *Listeria monocytogenes*

ECCO Statement OI 7F

Patients receiving immunomodulators are at risk of systemic and central neurological infections with *L. monocytogenes* [EL4]. The incidence appears higher in patients treated with anti-TNF therapy compared to other immunomodulators [EL 4]. Prevention includes avoidance of unpasteurised milk, cheese, uncooked meat, raw vegetables and smoked seafood [EL5]. Anti-TNF therapy should be discontinued during infection. A decision on restarting anti-TNF therapy should be taken in conjunction with an infection specialist and should involve a careful risk benefit.

See supplementary material.

Curative treatment consists of ampicillin, amoxicillin, or sulphamethoxazole/trimethoprim in case of allergy to penicillin.[310] No data are available on whether immunomodulators should be temporarily or indefinitely withheld in the event of active infection. Nevertheless, there are some reports of reinstitution of immunosuppression after treatment of active infection.[337]

7.5. *Nocardia* species

ECCO Statement OI 7G

Patients receiving anti-TNF therapy have been reported to be at risk of systemic and cutaneous infections with *Nocardia* spp., particularly when they are also treated with corticosteroids [EL4]. The risk of *Nocardia* spp. infections may be reduced by avoiding soil contact with broken skin and inhalation of soil-contaminated dust [EL5]. A decision on restarting anti-TNF therapy should be taken in conjunction with an infection specialist and should involve a careful risk benefit evaluation [EL5]

See supplementary material.

The patients should be treated with sulphamethoxazole/trimethoprim and/or ceftriaxone or carbapenems alone or in association and a specialist advice should be taken. It is advisable to prolong the antibiotics until the disappearance of all lesions.[344]

All immunocompromised patients and patients with neurological involvement are best treated for at least one year and some suggest indefinitely, especially if patients continue to be immunosuppressed as a result of their disease or treatment.[324] In order to obtain complete resolution of the infection, it has been suggested to indefinitely discontinue anti-TNFα treatment.[347,350]

7.6. Clostridium difficile infection

ECCO Statement OI 7H

Inflammatory bowel disease is an independent risk factor for infection with *Clostridium difficile*. Patients with colitis are particularly susceptible [EL3]

ECCO Statement OI 7I

Chemoprophylaxis for CDAD is not warranted. Hygiene procedures are recommended in a nosocomial setting [EL2]

ECCO Statement OI 7J

Screening for *C. difficile* is recommended at every flare in patients with colonic disease [EL3]. Diagnostic workup is recommended according to test availability and local practice. Available tests include glutamate dehydrogenase antigen and toxins A/B enzyme immunoassays, bacterial culture and cytotoxicity assay and nucleic acid amplification technology (NAT) tests

ECCO Statement OI 7K

Metronidazole and oral vancomycin are equally effective in treating mild to moderate CDAD [EL1]. It remains to be established if this applies to patients with inflammatory bowel disease. Other antibiotics should be stopped if possible. For severe CDAD, vancomycin has been shown to be superior in patients without inflammatory bowel disease [EL1] and is therefore preferable. In CDAD, use of immunomodulators should be guided by careful risk benefit evaluation and clinical judgement [EL4]

See supplementary material.

Immunomodulators are a known risk factor for *C. difficile infection* and development of CDAD. Experience from solid organ transplantation shows an increase in incidence and severity of CDAD after transplantation.[371] Glucocorticoids

and immunomodulators may also be independent risk factors for mortality in patients with CDAD.[372,373] In a large population-based cohort of IBD patients, corticosteroids, irrespective of dose and duration, were associated with a threefold increase in the risk of CDAD compared with other immunomodulator or biological agents.[374] Maintenance of immunomodulators, but not biologic therapy, was independently associated with CDAD in IBD.[365]

Antimicrobial stewardship, glove use, hand hygiene with soap and not alcoholic solution and disposable thermometers should be routinely used for the prevention of healthcare-associated *C. difficil*e infection.[375] Patients diagnosed with, or strongly suspected with infection, should be placed in isolation or cohorted together, when the number of cases is more than one.

In routine clinical practice, several different laboratory tests can be used to diagnose infection. Some of them detect the presence of toxins in the stools, such as the enzyme immunoassays (EIAs) and the cytotoxicity neutralisation assay (CCNA). Other targets the organism itself, such as the glutamate dehydrogenase (GDH) antigen assay or culture. Finally, molecular methods, such as nucleic acid amplification technology (NAT) tests, detect the presence of the toxin genes.[376] Some assays have also been created to test for hypervirulent strain, with reported high sensitivity and specificity.[377,378] There are numerous commercially available EIAs for both toxins A and B with good specificity but with lack of adequate sensitivity for sole use as a diagnostic modality.[362,379] Moreover, EIAs designed to detect only toxin A are likely to underreport the infection, since toxin A-negative *C. difficile* strains account for up to 3% of CDAD. EIAs for *C. difficile* GDH can be useful as initial screening in a multistep diagnostic approach.[362,376] NAT technology by amplifying the *C. difficile* toxin B gene could be used with high sensitivity and specificity.[380,381] Given its high sensitivity and the potential for false positive results, NAT test has been suggested in algorithms together with EIAs.[376] CCNA for *C. difficile* toxin B still represents the diagnostic gold standard despite its long turnaround time (24–48 h).[382] Endoscopy cannot be recommended as a diagnostic tool for CDAD[383]because pseudomembranes are only rarely found and their absence does not exclude infection. Pseudomembranes were only reported in 13% of hospitalised IBD patients with CDAD, a finding that was independent of immunomodulator use.[384]

In IBD patients, antibiotics use does not seem to play same role as in the general population and only a 43% rate of toxin-positive samples in active IBD patients with previous antibiotic has been reported.[354] Metronidazole is generally first line therapy for patients experiencing a first, or even a second episode of CDAD.[385] The usual oral treatment regimen is 200–250 mg four times daily or 400–500 mg three times daily for 10 to 14 days. Vancomycin (i.e., oral form) is highly effective for CDAD and preferable for multiple recurrences of CDAD, or if there is local resistance to metronidazole.[386] A recent meta-analysis showed no statistically significant difference in efficacy between vancomycin and metronidazole, or other antibiotics, including fusidic acid, nitazoxanide or rifaximin.[387] Similar results have been reported in another updated systematic review.[388] For patients with symptoms of severe CDAD, or if the patient's condition fails to improve or deteriorates on metronidazole, early use of vancomycin is recommended.[389] The dose of vancomycin for acute CDAD is 125 mg P.O. every 6 h, which is of equivalent efficacy to 500 mg four times daily.[390] To reduce the recurrence rate of CDAD, a tapered or pulsed (125–500 mg every three days for 2–3 weeks) treatment regimen with vancomycin has been proposed.[386] Other antibiotics, such as nitazoxanide and rifaximin, may be considered in case of recurrent disease.[353] Tigecycline, an intravenous antibiotic with good faecal penetration, has shown efficacy in the treatment of severe, complicated or refractory CDAD.[391] Data from a phase III trial showed that oral fidaxomicin (200 mg twice a day for 10 days) was not inferior to oral vancomycin in the treatment of mild to moderate CDAD. Moreover, significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence.[392] Fecal bacteriotherapy has been proposed in the treatment of recurrent CDAD, and a recent meta-analysis, including 27 studies with 317 patients, reported that fecal bacteriotherapy was generally effective.[393] Recurrent CDAD has been effectively treated by *Saccharomyces boulardii*, but evidence is still not sufficient to recommend probiotics.[394,395]

Thiopurine therapy, but not anti-TNFα therapy, has been significantly associated with *C. difficile* infection.[365] In a retrospective multicentre European cohort study 12% of patients given antibiotics and immunomodulators for CDAD associated IBD flare reached a composite endpoint of death or colectomy or in hospital megacolon, bowel perforation, haemodynamic shock or respiratory failure. None of the patients treated with antibiotics alone reached the endpoint ($p < 0.06$). The use of more than one immunomodulator increased the risk.[396] A recent survey among gastroenterologists, however, reported significant disagreement on whether combination of antibiotics plus immunomodulators or antibiotics alone should be given to IBD patients with CDAD-associated flares.[397] Clearly the risk and benefit of immunomodulator therapy should be balance in such patients, but it remains a matter of clinical judgment as to whether immunomodulators should be withdrawn. Steroids have been reported to be of therapeutic value in severe CDAD in a single small case-series[398] so there seems no reason to avoid corticosteroids.

8. Special situations

8.1. Patients travelling frequently or travelling to developing countries

ECCO Statement OI 8A

Inflammatory bowel disease need not restrict patients from foreign travel. Patients travelling to developing regions should have a pre-travel consultation. Special consideration should be given to patients on immunomodulators [EL5]. There is probably no overall increased rate of IBD flares after travel-related enteric infections [EL3]

ECCO Statement OI 8B

Pre-travel immunisation of IBD patients who are not on immunomodulators should follow standard guidelines for healthy travelers, according to travel destination [EL4]

ECCO Statement OI 8C

All patients with IBD should have Hepatitis A vaccination according to guidelines for the general population before travel to endemic areas. The normal two dose schedule should be completed, preferably before travel [EL5]. Response to Hepatitis A immunisation in IBD patients on immunomodulators should be checked by serological assay [EL5]

8.1.1. Guidelines for the IBD patient travelling to developing countries

The traveler with IBD is exposed to two main risks during travel:

(i) Relapse, exacerbation, or complications of the underlying IBD due to gastrointestinal infections acquired during travel, change in dietary habits, decreased compliance or unavailability of IBD medication.
(ii) Acquiring infectious diseases endemic to developing countries which may be more severe in IBD patients who are immunosuppressed.

These patients are therefore best advised to consult their gastroenterologist as well as a professional travel advisory clinic prior to travel.

8.1.2. Pre-travel consultation

Pre-travel interventions should be evaluated for both safety and efficacy. Patients with IBD should be provided with adequate medication, instructions for emergency self-treatment in the event of a disease exacerbation if medical assistance is not readily available and adequate health insurance, which includes cover for evacuation by air. Guidelines regarding vaccinations and preventive measures when travelling to less economically developed countries are frequently updated by the Infectious Diseases Society of America and the web sites and publications of CDC, eCDC and WHO.[399] Vaccine preventable diseases include: hepatitis A, hepatitis B, typhoid fever, yellow fever, Japanese B encephalitis, meningococcal meningitis, tick born encephalitis, poliomyelitis, influenza, mumps, measles, diphtheria, and tetanus. Malaria, traveler's diarrhoea, tuberculosis and insect-borne diseases, Influenza and sexual transmitted diseases (STD) are also considered.

This section addresses three principal questions:

1. Do these diseases behave differently when affecting IBD patients?
2. Do these diseases behave differently in IBD patients treated with IM/biologicals?
3. What is the degree of immunosuppression and what is its influence on the success of preventive measures and on their safety.

8.1.3. Do these diseases behave differently in IBD patients?

In a prospective case–control study of 71 IBD patients and their companions travelling to non-industrialised areas of the world, there was no increased rate of gastrointestinal infections among the IBD travelers, although mild increase in dermatological symptoms was noted.[400] Similarly, a retrospective case–control study of 222 IBD travelers and 224 healthy controls, found no difference between the IBD and the healthy groups in the rate of illness episodes during travel to the tropics or to developing countries.[401]

Although several epidemiological studies indicate that enteropathogens can provoke the initial onset of IBD and are associated with reactivation of quiescent disease,[402–404] a recent retrospective study did not show increased rate of IBD flares after traveling among 277 IBD patients, although only 43% of them were travelling to non-industrialised countries.[405]

8.1.4. Do travel-associated diseases behave differently in patients on immunomodulators?

In a recent prospective study of 75 travelers to developing countries who were receiving immunomodulator medications (21 on systemic steroids and 19 on anti TNFs) and additional 71 IBD patients of whom 69% were on immunomodulators, there was no travel-related preventable disease in any of these immuno-suppressed patients or in their healthy travel companions.[400] In another study, out of 277 Dutch IBD travelers of whom 43% were immunosuppressed, only 1 patient was admitted to the hospital with *salmonella enteritidis* gastroenteritis which responded to conservative therapy but no control group was reported.[405] In a retrospective case-control study, immunosuppressed IBD patients had a similar rate of illness during trips to the tropics as did healthy control group. A non-significant trend for increased illness episodes among immuno-modulator treated patients compared to controls (22% vs. 20%, P = 0.06) was observed when travelling to all developing countries were considered.[401] Finally, out of 75 immuno-suppressed renal transplant patients visiting developing countries, there were 4 illnesses requiring hospitalisation, of which 2 were definitely infectious (cellulitis in one, salmonella gastroenteritis in one)and both responded to standard therapy.[406]

In addition to these studies, there are only scant case reports regarding the contraction of travel-associated or vaccine-preventable infections by immunocompromised patients. These include a fatal poliomyelitis in one patient following administration of live oral polio vaccination to his daughter and 8 patients with malaria, of which one was fatal.[407] Anti-TNF drugs have been associated with reactivation of HBV in some patients and malaria (in one patient).

Thus, overall, it seems there is currently no documentation of direct effect of immunomodulators on the onset and severity of vaccine-preventable, travel-associated diseases in patients with inflammatory bowel disease. However, a detrimental effect of immunomodulation cannot be definitely excluded due to the rarity of these events.

8.1.5. The influence of immunosuppression on the safety and efficacy of preventive measures

Immunisation of patients with IBD against travel-associated vaccine-preventable diseases is highly desirable, because their altered immune status may predispose them to a more severe course of some vaccine-preventable infections. Two main issues have to be addressed when considering vaccination of patients with IBD on immunomodulators:

1. The safety of the vaccine and possibility of exacerbating IBD due to vaccination.
2. The efficacy of vaccination and modes of monitoring acquisition of immunity.

8.1.5.1. Vaccination safety. There are no reports of an increased rate of adverse outcomes following immunisation in patients with IBD not being treated with IMs. Furthermore, no vaccine has been shown to be associated with the initiation or exacerbation of IBD, despite speculation regarding the measles vaccine.[408] This is notable given the potential fatal outcome of measles in unimmunised patients, and in light of recent data from Germany showing that 45% of patients with IBD have not been vaccinated against measles (see below).[409]

Killed, inactivated or recombinant vaccines have been administered to many IBD patients with variable degrees of immunosuppression, as well as to other immunosuppressed patients (post-transplantation, rheumatic disorders, and chronic pulmonary disease). Adequate humoral responses to vaccination in immune-mediated inflammatory diseases has been demonstrated for hepatitis B, influenza and pneumococcal vaccination[410]

There are no reports of infectious complications caused by killed or inactivated vaccines and adverse events have been found to be similar to healthy controls. Therefore, clinical guidelines consistently advocate vaccination of immunosuppressed patients with inactivated vaccine for appropriate indications.[411–414] As a rule live vaccines are contraindicated in individuals until 3–6 after all immunomodulator therapy has been discontinued.

8.1.5.2. Efficacy of vaccination. Development of immunity following immunisation has been discussed in prior sections. However, it is of note that diminished cellular and humoral responses to the oral administration of Salmonella enteric serovar Typhi Ty21a vaccine was found among UC patients after colectomy compared to healthy individuals, presumably due to lack of colonic colonisation by the bacteria.[415] On the other hand, immunisation with oral inactivated B-subunit whole-cell cholera vaccine was similarly effective among UC patients after colectomy, compared to controls.[416] Thus, immunisation with parenteral inactivated *S. typhi* Vi polysaccharide is preferred in patients with inflammatory bowel disease who have had a colectomy and for those on immunomodulators.

Hepatitis A vaccine: In one study, eight liver transplant recipients were compared to 16 patients with chronic liver disease. None of the transplant patients responded to HAV vaccine, compared to 7 of 14 with chronic liver disease ($p < 0.02$).[417] In another study, 37 liver transplant recipients were compared both to healthy controls and patients with chronic liver disease. Maximal seroconversion of transplanted patients, observed at 7 months post-vaccination, was only 26%. No correlation was found with azathioprine or blood levels of calcineurin inhibitors.[418] Another study has reported seroconversion rates up to 41% in liver transplant patients and 24% in renal transplant patients after HAV immunisation.[419] In contrast with the transplant population data, a recent prospective controlled study in 66 pediatric IBD patients, of whom 49 were taking azathioprine and/or corticosteroids, the rate of seroconversion was similarly high after the second dose (>97%) in the IBD and the control groups, although the rate of seroconversion was lower in the IBD group when measured after the first dose.[420]

Measles vaccine: Measles can be severe or fatal in immunocompetent children and adults, especially pregnant women. Individuals with compromised immunity are at added risk of measles encephalitis and pneumonia, which can present insidiously, without rash, months after exposure. Measles remains endemic in many countries with regular outbreaks still occurring in Europe (http://www.who.int/immunization_monitoring/diseases/big_measlesreportedcases6months_PDF.pdf). Recent data from Germany show that 45% of patients with IBD have not adequate immunisation against measles.[409]

Evidence of immunity is provided by one of the following: (i) serological evidence of measles (measles IgG positive), (ii) being born before 1960 (virtually everyone had natural measles) or (iii) having documentary evidence of 2 doses of measles vaccine. Susceptible individuals should ideally be vaccinated prior to initiation of any immunomodulator therapy, and especially so if the patient is resident in, or anticipates travel to, a region where local outbreaks are occurring. The two dose schedule of measles-containing live virus vaccines, given 4 weeks apart, affords lifelong protection. Immunomodulator therapy can then be initiated 3 weeks or more following the second dose. When vaccination is not possible due to ongoing immunomodulator treatment, household contacts should be vaccinated so that the patient can be indirectly protected. Measles vaccine can safely be given to immunocompetent individuals without prior testing as additional doses do not pose a problem. It is important to establish measles-status even if vaccination is not feasible prior to immunomodulator therapy. This is to facilitate prompt administration of measles post-exposure prophylaxis with human immunoglobulin or intravenous immunoglobulin to susceptible immunocompromised patients.

8.2. Travellers' diarrhoea

ECCO Statement OI 8D

Patients with IBD are probably not more susceptible to traveller's diarrhea than healthy individuals [EL3]. They should pay close attention to precautions regarding food and water during travel. The immunocompromised patient should have a low threshold for initiating self-therapy for traveller's diarrhoea with quinolones or azithromycin [EL5]

8.2.1. Background
See supplementary material.

8.2.2. Treatment and self-treatment
See supplementary material.

8.3. Screening for latent tuberculosis

ECCO Statement OI 8E

The risk of M. tuberculosis infection in long term travellers to countries with high-endemicity is of similar magnitude to the average risk of the local population [EL2]. Patients with IBD traveling for more than a month to a moderately or highly endemic area should be advised to be screened for latent tuberculosis. If negative, screening should be repeated approximately 8–10 weeks after returning [EL5]

International travellers are at increased risk for tuberculosis, which may become evident months or years after travel. In a multicentre, prospective cohort study, the risk of *M. tuberculosis* infection in long-term immunocompetent travelers to high-endemicity countries, was substantial. It was of similar magnitude to the risk for the local population.[424] The clinician caring for patients with IBD may have to consider the following:

(i) Immunosuppression favors progression of asymptomatic latent tuberculosis to active disease.
(ii) IBD patients not treated with immunomodulators at the time of travel but who acquired (asymptomatic) TB infection during travel, may be considered for immunomodulators at a later stage.

Attempts should therefore be made to identify latent tuberculosis infection in these patients. Areas that are considered to be moderately to highly endemic for tuberculosis include most of the countries in Africa, Central America, South and Southeast Asia, the Middle East, the former states of the Soviet Union and parts of South America. Long-term (more than a month) travelers with IBD who had no screening test for latent tuberculosis or have a negative screening >1 year before traveling to these countries, are best advised to obtain a tuberculin skin test and/or interferon-gamma release assay (QuantiFERON TB-Gold test, or ELISPOT) before departure.[425,426] If the result is negative, the test should be repeated approximately 8–10 weeks after return.[427,428] A two-step tuberculin skin test (for patients on immunomodulators) is recommended initially, particularly if previous exposure is likely. A positive tuberculin skin test or interferon-gamma release assay is an indication for chest radiograph examination and treatment. These recommendations apply for the following IBD patients:

(i) Travelers with IBD to areas where tuberculosis is moderately to highly endemic and who are receiving immunomodulator therapy, regardless of the duration of travel
(ii) Travelers with IBD but without immunomodulators, who travel for at least one month to areas where tuberculosis is moderately to highly endemic
(iii) Travelers who might have prolonged exposure to patients with active tuberculosis (such as hospitalised patients, prisoners, or homeless population).

Particular consideration should be given to otherwise fit youngsters with IBD who travel abroad before or after University because they frequently travel for extended periods, stay in cheap accommodation or engage in welfare projects that might put them at higher risk. Of note, none of the current methods for pre- and post-travel TB screening approaches 100% sensitivity for diagnosing active tuberculosis.

8.4. Malaria

See supplementary material.

8.5. Prevention of insect bites

See supplementary material.

8.6. Guidelines for evaluating the returning traveler

ECCO Statement OI 8F

Returning travellers with diarrhea should have a stool examination for bacterial pathogens, ova and parasites and a complete blood count to identify eosinophilia. For long term travellers with IBD returning from countries highly endemic for strongyloidiasis, serological blood test for strongyloidiasis should be considered [EL5]

It is beyond the scope of these guidelines to review the large number of diseases that may affect the returning traveler. Consequently the focus of this section is on specific issues related to patients with IBD who return from developing countries (see Section 8.3 for screening for latent tuberculosis in the returning traveler).

8.6.1. General investigations
The returning traveler from long-term travel in developing countries who suffers from diarrhea should have a full blood count to identify eosinophilia, stool culture for enteric pathogens and microscopy for ova, cysts and parasites. This is particularly relevant to patients with IBD who are immunosuppressed.

The sensitivity of microscopic examination of a single stool specimen for the detection of ova, cysts and parasites generally exceed 80%.[429,430] Additional stool samples, as well as immunofluorescence or enzyme immunoassay for specific parasites, (e.g. *Giardia lamblia*, *C. parvum*, or *Entamoeba histolytica*) increase the sensitivity.[430,431] Parasitic infections are more likely to be diagnosed in patients with prolonged diarrhoea.[432] Common non-infectious causes of chronic diarrhoea in returning travellers include postinfectious disaccharidase deficiency, irritable bowel syndrome and undiagnosed latent disease such as villous atrophy. In many cases of

persistent diarrhoea, no known causative agent is identified, but symptoms usually resolve within one year.[430,433]

8.6.2. Strongyloidiasis

Strongyloidiasis deserves special consideration. In addition to non-inflammatory diarrhoea that is often associated with eosinophilia, *S. stercoralis* can produce overwhelming infection in immunocompromised persons, as a result of its unique ability to replicate and increase in numbers without leaving its host (autoinfection).[434] Strongyloidiasis can persist indefinitely in the host and cause hyperinfection years after acquisition when host immunity is impaired, especially by corticosteroid therapy.[435] IBD patients returning from endemic areas are best evaluated for possible strongyloidiasis, even in the absence of symptoms or eosinophilia. Strongyloidiasis in Europe may be more difficult to diagnosis in travel related infections than in immigrants.[436] and more severe in HTLV1 concomitant infected patients.[437] The sensitivity of a single stool examination is low and repeated stool examinations are often needed. The diagnosis is often made by serologic tests[256] (Table 1). Many experts recommend therapy for seropositive patients, despite negative stool examinations.

9. Pediatrics

ECCO Statement OI 9A

Children presenting with IBD under the age of five often have underlying immune deficiencies [EL4]. The present ECCO recommendations, that overall are applicable to the pediatric age group, should be interpreted with more caution in this group of patients [EL5]

ECCO Statement OI 9B

In infants whose mothers were treated with biologics during pregnancy, live vaccines should be withheld until at least the age of 6 months [EL4]

ECCO Statement OI 9C

In children with IBD, initial treatment at diagnosis with exclusive enteral nutrition offers a window to update the patients' vaccination status [EL5]

The overall recommendations regarding vaccinations should be applied to paediatric and adolescent patients, because, similar to adult IBD, they are also at increased risk of infections For the pediatric age group, some specific considerations are in needed.[29] Vaccination schedules are well established and regularly updated[438] but need to be reconsidered in cases of immune suppression.

In early onset IBD,i.e. under 5 years of age, underlying immune deficiencies should be highly suspected.[439–442]

Special consideration should be given to the immunisation of healthy infants whose mother receives biological treatments during pregnancy. A recent study reports that anti-TNFs (infliximab & adalimumab, but not certolizumab) crosses the placental barrier and that the drug can be found in cord blood and in the infant's serum for up to 6 months post-delivery.[443] A case of fatal systemic BCGitis from BCG vaccine in an infant born to a mother treated with anti-TNF has been reported.[444] Pediatricians should therefore avoid the administration of live vaccines to such infants during the first 6 months of life.[445]

In pediatrics exclusive enteral nutrition is considered a valuable alternative for induction therapy and could therefore be used as a window allowing time to complete and optimise immunisations prior to prescribing immunosuppressive agents.[446,447]

10. Vaccination and safety screening before starting an immunosuppressive treatment

ECCO Statement OI 10A

A standardised check list, screening for risk of opportunistic infections and adapted to local conditions, should be completed, preferably at the diagnosis of IBD [EL5]

ECCO Statement OI 10B

Vaccination history should be documented at diagnosis and immunisation status regularly updated [EL5]. Vaccination is best given before immunomodulator therapy [EL3]

10.1. Background

A standardized check list, screening for risk of opportunistic infections is implemented into the routine clinical care of patients with IBD since the emergence of the first consensus report on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease by the European Crohn's and Colitis Organization. These tools are adapted to the regional conditions and standards of care. The reduction of cases with tuberculosis during TNF inhibitor therapy after implementation of tuberculosis screening suggests that more comprehensive standardised screening programs might reduce the risk of other opportunistic infections associated with immunosuppressive treatment as well.

A standardised check list can be download from ECCO Website: ECCO website www.ecco-ibd.eu see publication (current link: https://www.ecco-ibd.eu/publications/ecco-guidelines-science/published-ecco-guidelines.html).

10.2. Detailed interview

Ideally the medical history should cover:

- History of bacterial infections (especially urinary tract infection)

- History of fungal infections
- Risk of latent or active tuberculosis: date of the last BCG vaccination; potential contact with patients having tuberculosis; country of origin, or prolonged stay in an area endemic for tuberculosis; history of treatment for latent or active tuberculosis
- History of varicella-zoster virus infection (chickenpox/shingles)
- History of herpes simplex virus infection
- Immunisation status for hepatitis B
- History of travel and/or living in tropical area or countries with endemic infections
- Future plans to travel abroad to endemic areas.
- Measles vaccination history

10.3. Physical examination

General physical examination best includes a search for features that often pass without comment, because they are of minor significance in people who are generally healthy, but which may have substantial implications when immunosuppressed:

- Systemic or local signs of active infection (including gingivitis, oral or vaginal candidiasis, or intertrigo as features of fungal infection)
- Cervical smear.

10.4. Laboratory tests

Some opportunistic infections are preventable and the potential for severe infection during immunosuppression can be ameliorated if thought is given to identifying risks before starting immunomodulator therapy. Baseline tests performed at diagnosis should include:

- Neutrophil and lymphocyte cell count; C reactive protein
- Urine analysis in patients with prior history of urinary tract infection or urinary symptoms
- Varicella zoster virus (VZV) serology in patients without a reliable history of varicella immunisation
- Hepatitis B and hepatitis C virus serologies
- Epstein–Barr virus serology
- Human immunodeficiency virus (HIV) serology after appropriate counselling
- Eosinophil cell count, stool examination and strongyloidiasis serology (for returning travellers)
- Hepatitis A virus and measles serologies (physician discretion).

10.5. Screening for tuberculosis

Screening for tuberculosis should be considered at diagnosis of IBD before using high dose corticosteroids or immunomodulators other than anti-TNF therapy, although it is considered mandatory for the latter group.

- Clinical context of risk (gathered from a detailed history, above)
- Chest radiograph
- Tuberculin skin test and/or interferon gamma release assay (according to country-specific guidelines).

10.6. Vaccination

Vaccines are best given before introduction of immunomodulator therapy. Consideration could reasonably be given to a vaccination programme at diagnosis of inflammatory bowel disease, since around 80% of patients will be treated with corticosteroids, 40% with thiopurines and 20% with anti-TNF therapy. As in the general population, the immunisation status of patients with inflammatory bowel disease should be checked and vaccination considered for routinely administered vaccines: tetanus, diphtheria, poliomyelitis. In addition, every patient with inflammatory bowel disease should be considered for the five following vaccines. Please refer to appropriate sections for dose and timing.

- VZV varicella vaccine (if there is no medical history of chickenpox, shingles, or VZV vaccination and VZV serology is negative
- Human papilloma virus
- Influenza (trivalent inactivated vaccine) once a year
- Pneumococcal vaccines (PCV 13 and PPSV 23)
- Hepatitis B vaccine.

Vaccines for patients on immunomodulators traveling in developing countries or frequently traveling around the world should be discussed with an appropriate specialist.

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Conflict of interest statement

ECCO has diligently maintained a disclosure policy of potential conflicts of interests (CoI). The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors (ICMJE). The CoI statement is not only stored at the ECCO Office and the editorial office of JCC but also open to public scrutiny on the ECCO website (https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html) providing a comprehensive overview of potential conflicts of interest of authors.

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References

See supplementary material.