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SPECIAL ARTICLE

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

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Opportunistic infections;
Prevention;
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Abstract

Background: In an era of increasing use of immunomodulator (IM) therapy, opportunistic infections have emerged as a pivotal safety issue in patients with inflammatory bowel disease (IBD). Today's challenge to the physician is not only to manage IBD, but also to recognise, prevent and treat common and uncommon infections.

Aim: To propose European guidelines on the management and prevention of opportunistic infections in patients with IBD.

Methods: The Delphi Consensus process was used to quantify expert opinion, with a systematic review of existing evidence. Infections were classified into major topics including virus (hepatitis C, hepatitis B, human immunodeficiency, herpes, human papilloma, JC and influenza viruses), bacteria (*Streptococcus pneumoniae*, *Legionella pneumophila*, *Salmonella* sp, *Listeria monocytogenes*, *Nocardia* sp, *Clostridium difficile*, *Mycobacterium tuberculosis*), parasites (*Strongyloides stercoralis*, *Toxoplasma gondii*) and fungal (*Aspergillus* spp, *Candida* spp, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Pneumocystis jiroveci*). Travel and vaccination policy were considered separately. IBD and infectious disease specialists were each assigned a topic. Groups performed a systematic literature review and made recommendations using grades and levels of evidence from the Oxford Centre for Evidence Based Medicine. All ($n=30$) met to fashion ECCO Statements at a 2 day face to face meeting; 80% agreement on wording meant that Consensus had been reached.

Results: A complete review of the impact of IM on the natural history, prevention, diagnosis, screening and treatment of specified infections was performed. Statements were agreed on screening and prevention of each agent, with specific recommendations on vaccination, travel, domestic and professional contacts, as well as a proposed work-up before IM therapy.

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Conclusion: ECCO guidelines provide clinicians with guidance on the prevention, detection and management of opportunistic infections in patients with IBD. Proposals may appear radical, potentially changing current practice, but we believe that the recommendations will help optimise patient outcomes by reducing morbidity and mortality related to opportunistic infections in patients with IBD.

Contents

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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, mainly azathioprine (AZA)/6-mercaptopurine (6-MP) and methotrexate (MTX), together with the advent of biological therapy. Immunomodulators are being used more often and earlier in the course of the disease.[1] The introduction of biologic agents, especially inhibitors of the key proinflammatory cytokine, tumor necrosis factor alpha (TNF-α) initiated a new therapeutic era, whose use has grown continuously since their introduction in 1998.[2] 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. Enhancing awareness and improving the knowledge of gastroenterologists about opportunistic infections are important elements to optimise patient outcomes through the development of preventive or early diagnostic strategies.

A long list of opportunistic infections has been described in patients with IBD. Many questions remain unanswered, not only concerning the need for screening, preventive measures or the best diagnostic approach, but also on appropriate treatment and management of immunomodulator therapy once infection occurs. This led the European Crohn's and Colitis Organisation

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(ECCO) to establish a Consensus meeting on opportunistic infections in IBD. The formal process of a Consensus meeting has been described,[3] but the purpose is to quantify expert opinion in the context of a systematic review of existing evidence. To organise the work, infections were classified into six major topics (see plan). Specific questions were asked for each infectious agent. The different topics were distributed to working groups that comprised junior and senior gastroenterologists with infectious disease experts. Each group performed a systematic review of the literature and answered questions on their topic, using recommendation grades and levels of evidence according to the Oxford Centre for Evidence Based Medicine. A two-day meeting in December 2007 with all participants fashioned the ECCO Statements after tough discussion (Anonymous, Centre for Evidence Based Medicine, Oxford. Levels of evidence and grades of recommendation. http://www.cebm.net/levels_of_evidence.asp.). This paper is therefore the product of work by gastroenterologists and infectious disease experts. It provides guidance on the prevention, detection and management of opportunistic infections in patients 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 proposals may appear relatively radical, with the potential for major impact on current practice, but we believe that these recommendations will help clinicians optimise patient outcomes by reducing morbidity and mortality related to opportunistic infections in patients with IBD. Since local antibiotic resistance, availability and practice varies, doses of specific drugs are not included. Local guidelines or specialist advice on dose and administration should be consulted as 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 defence barriers that permits microorganisms to cause either local or systemic infection.[4]

There is no clearcut definition of an immunocompromised state. Three categories are recognised by the Centers for Disease Control,[5] 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, leukaemia, lymphoma, generalised malignancy or therapy with alkylating agents, antimetabolites, radiation, or large 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* (conditions include hyposplenism and renal failure, among others.)

2.2. Definition of opportunistic infection

An opportunistic infection may be defined as a serious, usually progressive infection by a micro-organism that has limited (or no) pathogenic capacity under ordinary circumstances, but which has been able to cause serious disease as a result of the predisposing effect of another disease or of its treatment.[6] They are sometimes known as infections of unusual occurrence.

2.3. What makes an IBD patient immunocompromised?

ECCO Statement OI 2A
IBD patients should not be considered systemically immunocompromised in the absence of immunomodulatory therapy or malnutrition [EL5, RG D], despite evidence for a defect in mucosal innate immunity. IBD patients on different immunomodulators are probably not equally immunocompromised, but there is currently no single method of evaluating the degree of immunosuppression [EL5, RG D]

There is increasing evidence of an aberrant innate immune response occurring proximally and leading to T-cell activation in IBD.[7] Evidence includes decreased defensin expression by Paneth cells, impairment of neutrophil chemotaxis and decreased candidacidal or bactericidal functions. Changes in intestinal barrier function, downregulation of junctional complexes and defect in NOD2 pathways contribute substantially to defective innate immunity.[8,9] Description of the numerous mechanisms contributing to this dysimmunity is beyond the scope of this article. It is notable, however, that preliminary clinical trials of treatments that may stimulate immunity have yielded positive results, which further supports the concept of defective innate immunity in IBD.[10,11] 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, azathioprine, 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. Unfortunately there is no biological means of measuring the degree of immunosuppression in patients with IBD. According to the Centers for Disease Control, IBD patients belong to category '1' (Section 2.1).

2.4. Risk factors for developing an opportunistic infection

ECCO Statement OI 2B
Those particularly at risk for opportunistic infections are patients with combinations of immunomodulator therapies [EL3b, RG C] and those with malnutrition [EL4, RG D], which may be linked to disease severity. In addition, comorbidities should be considered. Age may be an independent risk factor for opportunistic infections in IBD [EL5, RG D]

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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.[6] In the IBD literature, very few data are available regarding risk factors for developing an opportunistic infection. Information was therefore collected from such IBD literature as there is, as well as 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 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, RG A]. 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 [EL2, RG B]

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. For example, an increased risk of granulomatous infections is generally attributed to anti-TNF therapy, but in a meta-analysis of serious infections during anti-TNF therapy, only 12 of the 126 reported infections were identified as granulomatous.[12] 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.[13] 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.[14] For corticosteroids there are no precise data in the IBD population that identify a dose associated with increased risk of infection. Nevertheless, the risk of postoperative infections has been clearly linked to concurrent use of corticosteroids in IBD patients undergoing elective surgery.[15] In rheumatologic patients, a dose-related, increased risk of infection is associated with concurrent corticosteroids.[16,17] The overall risk of infection increases for doses of prednisolone >10 mg/day, or cumulative dose >700 mg. In addition, a duration of steroid therapy >2 weeks predisposes to infections.[18]

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 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) of opportunistic infection if any one immunomodulator was used, increasing substantially (OR 14.5, 95% CI 4.9–43) if two or more drugs were used concomitantly).[13]

2.4.2. Exposure to pathogens and geographic clustering

ECCO Statement OI 2D
Exposure to pathogen is a risk factor for opportunistic infection in the immunocompromised population. Avoiding close contact with pathogens and endemic areas may be beneficial in reducing the risk of infection in IBD patients [EL5, RG D]. Special consideration should be given to patients from endemic areas, or patients who do not respond 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). 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.[19] Consequently special attention should be given to patients travelling to or living in areas of endemic infection. This is specifically addressed in Section 8. 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.[20]

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.[21] In this population, there is good evidence of functional alterations in cells from the innate and adaptative immune systems.[22–25] Despite this background, there is surprisingly little evidence that immune dysregulation has direct relevance to the infections commonly seen in the elderly population, except for reactivation of tuberculosis and decreased effectiveness of influenza vaccination in the elderly.

On the other hand, there are data to demonstrate that certain infections are more prevalent in the elderly than in younger adults. This increased prevalence ranges from 3–20 fold for community-acquired pneumonia and urinary tract infections respectively. The most commonly encountered infections in the elderly are from pyogenic bacteria. In

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contrast (and perhaps notable from an immunopathogenic perspective), viral infections are rare in comparison with the younger population, with the specific and again notable exceptions of influenza, reactivation of herpes zoster and viral gastroenteritis.[22]

Although increasing age is without doubt a risk factor for infection in the general population, it is surprising that this was not found in many series,[26,27] although, a single case–control study of 100 patients identified age >50 as a further predisposing factor (OR 3.0, 95% CI 1.2–7.2 relative to age <25 years). This is an important practical consideration.[13] It is of greatest importance to remain cautious when treating this subgroup of the IBD population, especially with anti-TNF therapy. Increasing age has also been identified as a significant predictor of infection in a cohort with rheumatoid arthritis.[16]

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.[16] No relevant comorbidities have been associated with infections in patients with IBD. It seems likely that this reflects the youthful age and limited co-morbidity of most patients with IBD, and as with age, pragmatic caution is again advisable when considering immunomodulator therapy in patients with comorbid conditions.

2.4.5. Malnutrition

Malnutrition appears to be the major cause of decreased immune function worldwide. It is not only a major risk factor for infection, but conversely chronic infection is itself an important cause of malnutrition, because it increases metabolic demand over a long period.[22] Without adequate nutrition, 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.[28]

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.[29] Immune disorders related to nutritional deficiency range from increased opportunistic infections and cancers to suboptimal responses to vaccinations.[28] Consistent with cause and effect, supplements of micronutrients improve immune responses, reduce the incidence of respiratory infections and ameliorate the impaired response to vaccination.[30] 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.[28] 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; sulphasalazine 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.[31]

Depressed cellular immunity has been observed in malnourished CD, both *in vivo* and *in vitro*.[32] Nevertheless, the correlation between malnutrition and risk of infection has not been extensively studied in IBD. Yamamoto found an increased risk of intra-abdominal septic complications in patients with an albumin level of <30 g/L.[33] 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.[34]

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 when starting immunomodulator therapy (or, indeed when considering surgery) in those with a BMI <20 kg/m^2 is something that rarely occurs to a gastroenterologist. Since nutritional support can reverse the impact of malnutrition on impaired immune function, it is a practical measure that should readily be implemented. The lack of evidence supporting this approach simply reflects the lack of research in this area.

3. Hepatitis C virus, hepatitis B virus and human immunodeficiency virus

3.1. Hepatitis C virus (HCV) infection

ECCO Statement OI 3A
No Consensus could be reached for HCV screening prior to starting immunomodulators. Immunomodulators are not necessarily contraindicated in active chronic HCV (HCVAb+, HCV RNA+). The decision depends on the severity of IBD and the stage of the liver disease
Acute HCV infection should be treated according to standard practice without stopping immunomodulators [EL5, RG D]

3.1.1. Background

The hepatitis C virus (HCV) is a hepatotropic RNA virus that belongs to the family flaviviridae. In Europe it is estimated that 0.2–2% of the population is infected with HCV. In most cases transmission of hepatitis C virus occurs parenterally. Sexual, perinatal, and sporadic transmission are reported, but infrequent. Acute HCV infection is often asymptomatic without jaundice. Chronic HCV infection develops in about 85% of all cases. Among patients with chronic HCV infection, 20% develop liver cirrhosis within

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20 years of disease duration, with a high rate of hepatocellular carcinoma (1–2% per year).

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

The effect of corticosteroids on the course of HCV infection in IBD patients has not been studied. Data from liver transplant patients suggest that slow tapering of steroids after liver transplantation for patients with HCV infection should be recommended, to improve HCV-related liver disease.[35] It is reasonable to assume, therefore, corticosteroids used in the treatment of IBD, have no detrimental effect on the course of HCV.

The impact of azathioprine on HCV infection in IBD patients has also not been evaluated. It has been demonstrated *in vitro* that azathioprine has antiviral activity against flaviviridae, including HCV.[36] Once again, extrapolating from patients undergoing liver transplantation for HCV infection, azathioprine can be used in IBD patients infected with HCV. As for methotrexate, a small series of hepatitis C patients with arthropathy showed no detrimental effect from treatment with methotrexate.[37]

Likewise, the role of TNF-α in the regulation and replication of HCV is unclear. Case series suggest that anti-TNF therapy has no adverse effect or might even improve HCV infection.[38–42] Peterson presented data on 22 HCV patients treated with either infliximab or etanercept for rheumatoid arthritis.[43] There were no significant differences between liver function tests and viremia assessments at baseline and follow up.

The best evidence that anti-TNF therapy might be beneficial for HCV infection comes from a study of etanercept as an adjuvant to interferon and ribavirin therapy for naïve patients with chronic HCV infection.[44] Anti-TNF strategy seems to improve virological response to a combined IFN-α_{2b}/ribavirin therapy in these patients.

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

Diagnostic approach and screening

No Consensus could be reached for HCV screening (including HCV antibody testing or HCV PCR in the event of positive antibody testing) prior to starting immunomodulators.

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 affect.[46]

3.1.5. 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 3B
HBV vaccination is recommended in all HBV seronegative patients with inflammatory bowel disease. Efficacy of hepatitis B vaccination is influenced by the number of immunomodulators given [EL3b, RG B]. Higher doses of the immunising antigen may be necessary to achieve success [EL3b, RG C]. Serological response should be measured after the completion of vaccination

ECCO Statement 3C
Before and during immunomodulator treatment, HBsAg+ carriers should receive pre-emptive therapy with anti-viral agents (nucleoside/nucleotide analogues) regardless of the degree of viremia in order to avoid hepatitis B flare [EL4, RG D]

ECCO Statement 3D
All IBD patients should be tested for HBV (HBsAg, anti-HBs, anti-HBcAb) to rule out HBV infection [EL5, RG D]

ECCO Statement 3E
Patients with evidence of chronic active HBV infection should receive standard antiviral therapy [EL1, RG B]. As IFN therapy might worsen underlying inflammatory bowel disease, nucleoside/nucleotide analogues should be used preferentially [EL5, RG D]

ECCO Statement 3F
There is no established treatment for acute HBV infection. Immunosuppressive therapy should be delayed until resolution of acute infection [EL5, RG D]

3.2.1. Background

Hepatitis B (HBV) virus is a hepatotropic DNA virus belonging to the Hepadna virus family. HBV is transmitted parenterally, sexually, and perinatally. Approximately 70% of patients with acute hepatitis B have anicteric or subclinical hepatitis, while the remainder present with icteric hepatitis, or occasionally fulminant hepatic failure. The rate of progression from acute to chronic hepatitis B depends largely on the age of infection. It is estimated at 90% for infection acquired perinatally and 20–50%, or 5% for infection at age 1–5 years or during adulthood, respectively.[47–50] Chronic hepatitis B is

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characterised by viral replication in hepatocytes and the immune response towards the virus, with consequent hepatitic necrosis and inflammatory response. The early phase of chronic HBV infection features high viral replication associated with active liver disease, while the later, low replicative phase is characterised by remission of overt liver disease. In contrast, patients with perinatal HBV infection exhibit another clinical course during their early decades, with active viral replication and the absence of hepatic injury, which is considered an immunotolerant phase of disease. It is important to note that even in patients who recover from acute hepatitis B, HBV DNA is still detectable in the hepatocytes of most patients.[51] In some of these patients traces of HBV DNA are detectable in peripheral blood many years after resolution of acute hepatitis B.[52,53]

A flare of HBV infection refers to an abrupt increase transaminases in patients with chronic hepatitis B. Acute flares reflect an increase in the immune response against HBV, which might explain why flares of disease are predominantly associated with withdrawal of immunosuppressive therapy (e.g. corticosteroids or cytotoxic agents). They rarely occur during immunosuppression. Indeed, corticosteroid 'priming' (a deliberate short course of corticosteroid treatment followed by abrupt withdrawal) has been evaluated as a strategy to increase the response rate towards antiviral therapy in HBV, although ineffective. Post-steroid flares have been associated with hepatic decompensation.

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

The effect of corticosteroid, immunomodulator, or anti-TNFα therapy on the course of HBV infection in IBD patients has not been studied prospectively. Consequently, recommendations for the management of chronic HBV infection during immunomodulator therapy are based on observations in patients undergoing treatment for other chronic inflammatory conditions, or cytotoxic treatment of solid tumors or haematologic malignancies, as described by societies including the American Association for the Study of Liver Disease (AASLD).[54] Data derived from HBsAg+ cancer patients indicates that reactivation of HBV replication occurs in 20–50% of hepatitis B carriers undergoing immunosuppressive or cancer chemotherapy. Most are asymptomatic flares, but icteric flares and even hepatic decompensation or death have been observed.[54] Reactivation of HBV replication in patients treated for lymphoma are more common when chemotherapy regimens include corticosteroids.[55] There are case reports of symptomatic and severe HBV flares in HBsAg+ IBD patients receiving infliximab.[56–58] One report has described HBV reactivation in an anti-HBcAb+ and HBsAg− patient.[59]

3.2.3. Preventive measures

Seronegative patients

HBV vaccination is recommended in all seronegative IBD patients, because of the potential consequence of steroids or immunomodulator therapy should HBV be acquired. It is reasonable to take the risk of acquiring HBV into account.

Seropositive patients with prior evidence of HBV infection

HBsAg+ patients: In chronic HBsAg+ carriers, prophylactic antiviral treatment with nucleotide/nucleoside analogues is recommended, best started 2 weeks prior to the introduction of steroids, azathioprine, or anti-TNFα therapy and continued for 6 months after their withdrawal. In line with recommendations from AASLD, 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. Most data exists for lamivudine, but other nucleotide/nucleoside analogues may be used. If immunomodulator therapy (such as azathioprine) is expected to last >12 months, nucleotide/nucleoside analogues with a lower propensity than lamivudine for provoking drug-resistant mutations of HBV DNA might be preferred. Interferon-alpha (IFNα) is best avoided for two reasons: first, IFNα may exacerbate Crohn's disease and second, IFNα may cause additional bone marrow suppression.

HBsAg− patients: 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. Since this is infrequent and information in the patient population receiving cytotoxic or immunosuppressive therapy is limited, routine prophylaxis for these individuals is not recommended.[60,61] Such patients should be monitored routinely for elevation of AST/ALT, as well as for changes in HBV serology and HBV DNA as clinically indicated.

3.2.4. Diagnostic approach, screening and treatment of underlying infection

Diagnostic approach and screening

All IBD patients are best tested for HBV infection (HBsAg, anti-Hbs Ab, anti-HBcAb) to assess infection or vaccination status. In patients presenting with evidence of HBV infection, HBeAg, anti-HBe, and HBV DNA should be assessed as recommended by local guidelines for the management of HBV.

Treatment of chronic HBV infection

Treatment with IFN-α of chronic active HBV infection and concomitant Crohn's disease is generally not recommended, because IFN-α may exacerbate Crohn's disease. Patients with ulcerative colitis and concomitant HBV infection may receive IFN-α, since an adverse effect on the course of IBD is less likely.[46] Nucleotide/nucleoside analogues have not been tested in IBD patients on immunomodulator treatment, but case series suggest that they are safe and effective.

3.2.5. Infection occurring during immunomodulator therapy

There are no reports of newly acquired (acute) HBV infections 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 adults resolves in the vast majority of patients. Corticosteroids may increase the replication rate of HBV by direct effects on viral replication as well as inhibition of the immune response and might worsen disease or increase the chance of chronic infection. The effect of immunomodulators on acute HBV infection has not been studied prospectively.

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3.3. Human immunodeficiency virus (HIV) infection

ECCO Statement OI 3G
Testing for HIV should be considered for patients with inflammatory bowel disease prior to starting immunomodulator therapy, based on anecdotal reports of increased risk and severity of HIV-related infections in patients receiving immunomodulator therapy [EL4, RG D]. Re-testing is indicated for patients at high-risk

ECCO Statement OI 3G
Testing for HIV should be considered for patients with inflammatory bowel disease prior to starting immunomodulator therapy, based on anecdotal reports of increased risk and severity of HIV-related infections in patients receiving immunomodulator therapy [EL4, RG D]. Re-testing is indicated for patients at high-risk

ECCO Statement OI 3H
The diagnosis of inflammatory bowel disease in HIV-positive patients, should be reviewed and treatment managed in conjunction with appropriate specialists [EL5, RG D]. Treatment of HIV in patients with inflammatory bowel disease, including chemoprophylaxis, should follow standard guidelines [EL1, RG B]. Immunomodulators are not necessarily contraindicated in HIV-positive patients [EL4, RG D]

3.3.1. Background

The human immunodeficiency virus (HIV) belongs to the human retrovirus family. The hallmark of HIV is transcription of its genomic RNA to DNA by an enzyme called 'reverse transcriptase'. Infection is mediated by binding of viral gp120 to the CD4 co-receptor that is expressed on the surface of CD4+ T helper cells, monocytes/macrophages and dendritic cells. Certain co-receptors such as CCR5 and CXCR4 are mandatory for viral entry. The consequence is a progressive quantitative and qualitative deficiency of T-helper cells and a subsequent impairment of T-cell mediated immune responses. If T-helper cell concentrations ultimately decline below a certain threshold, patients are at high risk of developing opportunistic diseases, including infections and malignancies that are AIDS-defining illnesses. Transmission of HIV occurs by homo- or heterosexual contact, blood or blood products and by infected mothers to their infants, whether intrapartum, perinatally, or via breast feeding. The clinical manifestations of HIV infection comprise a broad spectrum from an acute HIV syndrome associated with primary infection, to a prolonged phase of clinical latency, to the state of symptomatic advanced disease. Thanks to highly active anti-retroviral therapy (HAART), viral replication can be effectively suppressed, so that an almost normal immune status can be regained in HIV-infected patients.

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 not been studied. Corticosteroids are known to decrease CD4+ counts after acute administration, which may be a consequence of redistribution of leukocytes. Chronic corticosteroid administration has a lesser effect.[62] Nevertheless, corticosteroids are used as adjunctive therapy in the treatment of complications of HIV infections such as lymphoma or *Pneumocystis jiroveci* infection.[63] A single centre study investigated the effects of 40 mg/day prednisolone as an adjunct to antiretroviral therapy in 24 HIV-infected subjects with >200 CD4+ T cells/mm^3 in a randomized placebo-controlled trial. After 8 weeks, no effect was observed on markers of T-cell activation or apoptosis. Two subjects assigned to prednisolone were subsequently found to have asymptomatic osteonecrosis of the hip. The authors concluded that the potential role of corticosteroids as adjunct therapy will be limited by concerns regarding their toxicity; however, further studies of other agents to limit cellular activation in AIDS are warranted.[64] 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.

Azathioprine and its effect on HIV infection in IBD patients have also not been evaluated. Anecdotal evidence suggests that treatment with azathioprine leads to exacerbation of HIV disease and should be avoided.[65] However, there is one case report describing long-term non-progressive HIV-1 infection and excellent graft survival in a patient after renal transplantation receiving a conventional immunosuppressive regimen, namely azathioprine and prednisolone.[66] No data on the use of azathioprine in patients with IBD and active or successfully treated HIV infection are available, so as with steroids, carefully monitored treatment is appropriate if necessitated by the clinical pattern of IBD.

TNF-α has been implicated in the pathogenesis of HIV infection, by contributing to HIV replication through activation of NF-κB.[67] 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,[68] may even accelerate the disease.[69] There are, however some studies on the effects of anti-TNF-α therapy on the course of HIV infection which have been reviewed.[70] These small studies of 6–11 patients have indicated that neither infliximab nor etanercept in single (etanercept) or double doses (infliximab 10 mg/kg two weeks apart) worsened HIV infection. A third study investigated the effect of a four week therapy with etanercept (25 mg twice weekly) in 16 untreated HIV patients with smear positive

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tuberculosis and CD4+ cells >200/mm^3. The clinical response to anti-tuberculous chemotherapy was at equivalent or superior to a historical treatment group,[71] 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 co-existing HIV infection and might not have the detrimental effects on HIV infection that theory might suggest.[72]

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

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 active infection, because of the potential consequence of such therapy should HIV be acquired. It is reasonable to take the risk of acquiring HIV into account.

Treatment of the infection

Due to the lack of clinical data on the effect of immune-reconstitution following treatment with HAART on the course of concomitant HIV and IBD, no recommendations are available.[70] 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. However, the different immunopathology of Crohn's disease and ulcerative colitis may mean that the effects and benefits of HAART on the underlying IBD may also differ.

The susceptibility to infection of IBD patients suffering from HIV greatly depends on the success of HAART. When the CD4+ count is >350/μl the risk may be little different to those without HIV. 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

There are no reports of acute HIV infections during immunomodulator or biological therapy. From a practical point of view, symptomatic HIV infection should be treated according to current guidelines. 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, JC virus and influenza virus

4.1. Cytomegalovirus (CMV) infection

ECCO statement OI 4A
Screening for a latent or subclinical CMV infection is not necessary before starting immunomodulator therapy [EL2, RG B]. Latent or subclinical CMV infection is no contraindication for an immunomodulator therapy [EL2, RG B]. CMV colitis should be excluded, preferably by tissue PCR or immunohistochemistry, in immunomodulatory refractory cases of IBD before increasing immunomodulator therapy [EL3, RG C]. In case of severe colitis with CMV detected in the mucosa during immunomodulator therapy, antiviral therapy should be initiated and discontinuation of immunomodulators considered until colitis symptoms improve. In case of systemic CMV infection immunomodulator therapy must be discontinued [EL2, RG B]

4.1.1. Background

The majority of primary infections with CMV are asymptomatic. Clinically apparent infections may present as a mononucleosis-like syndrome, but can affect virtually any organ.[73,74] Although CMV may persist in a latent form after primary infection, development of severe CMV-related disease during or after immunosuppressive therapy is rare in IBD. There is, however, a risk of hepatitis, colitis, oesophagitis, pneumonia, encephalitis or retinitis.[73–75] Although CMV has a world-wide distribution, the prevalence of CMV is higher in developing countries, or areas with poor socioeconomic conditions. This is probably related to closer physical contact, since CMV is transmitted via close personal contact with affected persons excreting the virus in their body fluids, or shedding from throat or uterine cervix.[74] 10–20% of children are infected with CMV before puberty and CMV seroprevalence increases after infancy to 40–100% in adults.[74,76] CMV colitis mimicking an acute exacerbation of ulcerative colitis (UC) or Crohn's disease (CD) is associated with a poor outcome and a higher colectomy rate.[77–79]

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.[80] This reactivation is usually asymptomatic, or characterised by a mild, self-limited course. Serious tissue damage is very rare.[73,81] 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).

Several studies have suggested an association between infection with CMV and steroid- or therapy-resistant IBD and complications, including toxic megacolon.[78,82–91] A causal relationship, however, has not been proven. CMV infection is common in immunocompromised patients with IBD, but not

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Table 1 Sensitivity and specificity of different techniques for diagnosis of CMV infection.[80]

Method		Sensitivity (%)	Specificity (%)
Histology	H&E staining	10–87	92–100
	Immunohistochemistry	78–93	92–100
Serology	CMV IgM	100	99
	CMV IgG	98–100	96–99
Viral culture	Conventional	45–78	89–100
	Shell vial culture	68–100	89–100
Antigenaemia assay		60–100	83–100
DNA tests	PCR	65–100	40–100

all CMV infections lead to clinical disease.[92] Matsuoka has demonstrated that CMV is frequently reactivated in patients with UC treated with steroids or 6-mercatopurine, but disappears without antiviral therapy.[93] In their series, CMV antigen 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.[94–96] 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.[73,74,80]

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

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. Different techniques for the diagnosis of CMV infection are available (Table 1). 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).[74,76,97] Conventional viral culture and the faster shell vial culture are highly specific, but have disadvantages including long incubation, lack of viral quantitation, 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.[74,97] The most commonly used technique for diagnosis of CMV infection and disease is detection of CMV DNA through PCR. 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, stool) and applicability in neutropenic patients.[74,76,97]

In patients with severe colitis, CMV has been reported in colonic tissue in 21–34% and in 33–36% of steroid-refractory colitis.[80] 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.

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.[80,81] In cases of ganciclovir resistance or intolerance (e.g. myelotoxicity), foscarnet (for 2–3 weeks) is an alternative.[80,81,98]

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. Severe, systemic CMV reactivation causing meningo-encephalitis, pneumonitis, hepatitis, oesophagitis, or colitis, is rare, but associated with a poor outcome.[77,79,80] Prompt antiviral treatment with ganciclovir or other agents and discontinuation of immunosuppressive agents is associated with clinical improvement and decreased mortality,[77–80] so are recommended.

4.2. Herpes simplex virus (HSV)

ECCO statement OI 4B
Screening for latent HSV infection or chemoprophylaxis before onset of immunomodulator therapy is unnecessary [EL2, RG B]. Past or latent HSV infection is no contraindication to immunomodulator therapy [EL2, RG B]. In case of recurrent labial or genital HSV infection, oral antiviral therapy should be considered during immunomodulator therapy [EL2, RG C]. HSV colitis is best excluded by immunohistochemistry or tissue PCR as a cause of immunomodulatory refractory IBD before increasing immunomodulator therapy [EL4, RG D]. In the event of severe HSV during immunomodulator therapy, antiviral therapy should be initiated and immunomodulators discontinued till improvement of symptoms [EL4, RG C]

4.2.1. Background

Primary infection with HSV in immunocompetent individuals usually causes an asymptomatic or mild, self-limited oral–labial (generally HSV type 1) or genital (generally HSV type 2) infection, followed by latent HSV persistence in nerve ganglia.[75,99] Seroprevalence for *Herpes simplex* virus type 1

(HSV-1) and type 2 (HSV-2) depends on different factors including age, gender, country, region within the country and population subgroup. The worldwide prevalence of HSV-1 by the fourth decade is 45–98%.[99] HSV-2 seroprevalence correlates with age and gender (higher in women), rising with initiation of sexual activity in adolescence and increasing through adulthood.[100] It is negligible under the age of 12 years, increases to a peak between 15 and 24 years of age and declines with advanced age.

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

In immunocompromised individuals HSV infections have a greater potential for dissemination.[75] HSV reactivation may cause severe systemic infections associated with significant morbidity and mortality including encephalitis, meningitis, pneumonia, oesophagitis, colitis, or hepatitis.[101–106] Cell-mediated immunity appears to be the dominant process for controlling viral replication.[100] Recurrent oral or genital herpes may be both more frequent and severe in immunocompromised patients.[107]

4.2.3. Preventive measures

There is no vaccine available for HSV. Chemoprophylaxis for HSV infection is unnecessary for the same reasons as CMV (Section 4.1.3). In the event of recurrent labial or genital HSV infection, oral antiviral therapy should be considered: aciclovir 400 mg twice daily, valaciclovir 500 mg daily, or famciclovir 250 mg twice daily are appropriate.[108]

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

Diagnostic approach and screening

The presence of high titres of anti-HSV IgG in the serum, the appearance of HSV-specific IgM, or increasing titres of anti-HSV IgG, are indicators of relapsing HSV infection, but only few patients with recurrent HSV infection show a large increase in the HSV antibody titre. Serologic detection of HSV antibodies indicates prior exposure to HSV, but is inadequate for diagnosis. The diagnostic gold standards for HSV infection is PCR or IHC from affected tissue or biopsies.[99] Screening for latent HSV-infection in IBD patient is not indicated.

Treatment of the infection

The nucleoside analogue aciclovir is effective therapy.[75,107] Aciclovir selectively inhibits the replication of herpesviruses by inhibiting the viral polymerase after intracellular uptake and conversion to aciclovir triphosphate.[109] Other antiviral drugs for the treatment of HSV infection are valaciclovir, a prodrug of aciclovir, penciclovir, or its prodrug famciclovir.[75,107]

4.2.5. Infection occurring during immunomodulator therapy

Since most cases of systemic HSV reactivation in immunocompromised patients are subclinical or run a mild, self-limited course, they do not require discontinuation of immunomodulators or systemic antiviral therapy.[110] Nevertheless, immunomodulators should not be initiated during active HSV infection, since it may exacerbate or disseminate during immunosuppressive therapy.[75] Thought should be given to the potential for disseminated HSV infection when considering azathioprine in a patient with active labial or genital HSV. Severe HSV infection causing hepatitis,[101,104,111] encephalitis,[112] colitis,[102,106,111,113] or pneumonitis[104,114] during immunosuppressive therapy for IBD are extremely rare. Antiviral therapy with intravenous aciclovir or alternative (Section 4.2.4) and discontinuation of immunosuppressants are appropriate.[102,106,113] HSV colitis is very rare even in patients with IBD, but it might cause or mimic an acute relapse.[102,106,111,113] The risk of colectomy is high.[106]

4.3. Varicella zoster virus (VZV)

ECCO statement OI 4C
If the medical history of chickenpox, shingles and VZV vaccination is negative, immunisation with VZV vaccine should be performed at least 3 weeks before onset of immunomodulator therapy, and preferably at diagnosis of IBD [EL5, RG D]. Previous VZV infection is not a contraindication to immunomodulator therapy, but should not be started during active infection with chickenpox or herpes zoster [EL4, RG D]. In the event of VZV infection during immunomodulator therapy, antiviral treatment should be started [EL1, RG B] and immunomodulator therapy discontinued in severe cases if possible [EL5, RG D]. Reintroduction of IM therapy is possible after vesicles and fever have resolved [EL5, RG D]

4.3.1. Background

Unlike other herpesviruses, primary infection with VZV is nearly always symptomatic. It causes chickenpox (varicella), characterised by fever, malaise and typical vesicular skin lesions[115] and after reactivation of latent VZV in dorsal root ganglia, herpes zoster (shingles) may develop. In the prevaccine era almost all children became infected by the age of 15 years.

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

Reactivation of VZV is mainly found in patients aged >50 years or immunocompromised patients. It typically manifests as a painful, unilateral, vesicular rash distributed in one or more dermatomes. Immunosuppression increases the risk of dissemination and complications such as pneumonia, hepatitis, encephalitis, or haemorrhagic disorders (thrombocytopenia or disseminated intravascular coagulopathy).[115,116]

4.3.3. Preventive measures

For children with IBD not on immunomodulator therapy, recommendations for immunisation are the same as the general population.[117] Depending on local guidelines, routine live-virus VZV vaccination is given at the age of 12–18 months with a booster at 11–12 years of age.[115–118]

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For immunocompromised children, including those on high-dose corticosteroids (14 day course of prednisolone >2 mg/kg pr (or equivalent), or a total of ≥20 mg prednisolone/day for children with a weight >10 kg), live-virus vaccine is contraindicated until immunomodulators have been discontinued for at least 3 months.[118]

Unimmunised, immunocompetent adults with IBD should best receive active immunisation with a 2-dose series of live varicella vaccine at least 3 weeks before immunomodulators are started.[115,118]

Passive immunisation with a high-titre preparation of VZV IgG antibodies (VZIG) is appropriate for unimmunised, seronegative, high-risk patients with IBD (immunosuppression, pregnancy) who have had close exposure to a person with chicken pox or herpes zoster. VZIG should be given within 96 h of exposure in a recommended dose (125 units, or 1 vial/10 kg of body weight to a maximum 625 units).[115,117,118] After administration of VZIG, patients should be observed for 28 days. In the event of clinical symptoms of VZV infection, immediate antiviral therapy should be initiated[118] although specialist advice is best taken.

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

Diagnostic approach and screening

VZV has a worldwide distribution, with a preference for temperate climates, where seroprevalence is >90% in adults.[115] Serology is of limited value for the diagnosis of acute VZV infection, because testing for VZV IgM and IgG antibodies lack specificity and sensitivity.[115] Nevertheless, detection of VZV IgG antibodies reliably determines former VZV infection if a history of varicella is unknown or uncertain. PCR, viral culture and IHC or hybridization methods are more sensitive for confirming a diagnosis of current VZV infection or reactivation if there is clinical uncertainty.[115,116]

Treatment of the infection

Aciclovir for chickenpox and zoster and valaciclovir or famciclovir for zoster are licensed antiviral agents. Alternatives in aciclovir-resistant cases are foscarnet.[115]

4.3.5. Infection occurring during immunomodulator therapy

Primary infection or reactivation of VZV during immunomodulator therapy leading to chickenpox or herpes zoster is uncommon.[26,110,119–124] Immunomodulators should not be initiated during chickenpox or shingles. Recurrent herpes zoster, depending on the severity or frequency, is a relative contraindication to immunomodulators.[115]

Only a few cases of severe varicella or herpes zoster associated with immunomodulators in IBD or rheumatoid arthritis have been reported, but most experienced clinicians have seen or heard of a case. However, disseminated VZV should be considered a medical emergency and treated as soon as possible. Except for 3 fatal cases,[125–127] all patients recovered after intravenous antiviral therapy with aciclovir. In some cases, immunomodulators were temporarily discontinued[121,128–138] until improvement of clinical symptoms, then restarted without further problems.

4.4. Epstein–Barr virus (EBV)

ECCO statement OI 4D
Screening for latent or subclinical EBV infection or chemoprophylaxis before onset of immunomodulator therapy is not recommended [EL2a, RG B]. In severe clinical EBV infection during immunomodulator therapy, antiviral therapy should be initiated and immunomodulator therapy discontinued [EL4, RG D]. In the event of EBV-related lymphoma during immunomodulator therapy, immunomodu- lators should be stopped, because discontinuation of immunomodulators often leads to spontaneous regression. In case of absent spontaneous regression or progression of lymphoma after interruption of immunomodulators chemotherapy should be considered [EL4,RGD]

4.4.1. Background

Like other members of the herpesvirus family, EBV infects more than 90% of the world's adult population, regardless of geographical location. EBV seropositivity increases with age (>96% when over 60 years of age).[139–141] Primary EBV infection is often asymptomatic, or causes infectious mononucleosis, which usually takes a mild and self-limiting course. After primary infection EBV remains latent in circulating B lymphocytes for life.[139–141]

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

EBV infection has been associated with the development of neoplasia, including lymphoma, sarcoma and carcinoma, especially in those who are immunocompromised.[142] Several studies have shown the potential for self-limited reactivation of latent EBV infection after introduction of immunomodulators, without provoking symptoms or serious EBV-associated disease.[95,96,143,144] Nevertheless, some data suggest that even a transient increase in EBV DNA load may increase risk of lymphoma.[95,144] An EBV load of >1000 copies per 500 ng DNA of peripheral blood mononuclear cells (PBMCs) seems to be associated with an increased risk of lymphoproliferative disorders in heart transplant patients.[143]

4.4.3. Preventive measures

No EBV vaccine is available. Chemoprophylaxis is not recommended, because reactivation during the treatment of IBD leading to serious clinical disease is exceptionally rare.

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

Diagnostic approach and screening

Serological diagnosis of EBV infection use direct immunofluorescence against IgG or IgM antibodies targeting EBV capsid antigen (VCA), as well as IgG antibodies specific for EBV nuclear antigen 1 (EBNA 1). Primary EBV infection is confirmed by detection of VCA IgM in the

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absence of EBNA 1 IgG. Recent EBV infection is detected by EBNA 1 IgG without VCA IgM. However, VCA IgM antibodies may be undetectable, or their appearance may be delayed during active infection. Diagnosis is further complicated because VCA IgM may persist for several months after infection. Therefore RT-PCR is both more reliable and more sensitive for early, definitive diagnosis of EBV, especially in serologically indeterminate EBV infections.[145,146]

Treatment of the infection

In most cases EBV infection does not require antiviral treatment and in normal people the clinical benefit of antiviral therapy for infectious mononucleosis has not been established.[147] In the event of severe EBV-associated disease, therapy with aciclovir or ganciclovir may be given, but efficacy against EBV is not as high as for CMV, HSV or VZV.[75,148] Specialist advice is appropriate.

4.4.5. Infection occurring during immunomodulator therapy

Only two cases of fatal infectious mononucleosis after primary EBV infection associated with azathioprine therapy in patients with Crohn's disease (CD) have been reported.[149,150] When severe EBV-associated disease occurs in immunocompromised patients, antiviral therapy with aciclovir or ganciclovir is best initiated promptly, despite the lesser efficacy compared to other herpesviruses. It is possible that ganciclovir is more potent than aciclovir for EBV infection and may help prevent lymphoproliferative disorders, but further data are necessary.[148]

A higher rate of lymphoma has been reported in patients with IBD, especially if treated with immunomodulators, compared to the general population.[151,152–169] In transplant recipients, a viral load of >1000 copies of EBV per 500 ng DNA from PBMCs may be a marker for an increased risk of EBV-associated lymphoproliferative disorders.[143] Discontinuation of immunosuppressive therapy often results in spontaneous regression of EBV-associated lymphoma.[157,165] Prophylaxis with aciclovir or ganciclovir after renal transplantation has been reported to reduce the risk of lymphoma in renal transplant recipients,[148] but the risk of lymphoma is too low to justify this approach in IBD.

4.5. Human papilloma virus (HPV)

ECCO statement OI 4E

Regular gynaecologic screening for cervical cancer is strongly recommended for women with IBD, especially if treated with immunomodulators [EL2a, RG B]. In patients with extensive cutaneous warts and/or condylomata, discontinuation of immunomodulator therapy should be considered [EL5, RG D]. Routine prophylactic HPV vaccination is recommended for women according to national guidelines [EL2a, RG B]. Current or past infection with HPV is no contraindication for immunomodulator therapy [EL2a, RG B]

4.5.1. Background

Human papillomavirus (HPV) is the most common sexually transmitted infection in the world.[170] The distribution varies widely, depending on gender (higher in women than in men), geographical region (higher in poor countries), age, sexual behaviour and viral type, as well as the methods and site of detection.[171,172] About 40 types of HPV are sexually transmitted. They are classified into low-risk types, associated with anogenital warts or mild dysplasia, and high-risk types associated with high-grade dysplasia and anal neoplasia (cervical and anal carcinoma).[173,174] Cutaneous warts are also caused by HPV.

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

Immunomodulators do not generally aggravate the course of the disease, but there is concern that HPV-associated tumors may be more common after years of immunomodulator therapy.

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.[175,176]

Depending on local guidelines, routine HPV vaccination is recommended for females aged 11–12 years before onset of sexual activity. In the event of missed or delayed vaccination, HPV vaccination is also recommended for females aged 13–18 years. It is not recommended for males, females aged younger than 9 years, or older than 26 years because the efficacy, safety and cost-effectiveness of HPV vaccination in these cohorts has not been established.[177–181] HPV immunisation uses a non-live agent, so it may be administered to immunocompromised IBD patients.[117]

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

Diagnostic approach and screening

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.[182,183] 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.[184]

Cervical smear testing in immunocompromised women is recommended as for the general population.[185,186] 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.[170]

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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.[185,187]

4.5.5. Infection occurring during immunomodulator therapy

Two 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.[188,189] Therefore 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.[190] They may be considered candidates for HPV vaccine regardless of their sexual history.[188,189] Nevertheless, infection with HPV is no contraindication to immunosuppression.

Anal carcinoma and squamous cell carcinoma (SCC) in particular are considered to rare complications of IBD (perhaps more common in those with chronic fistulating Crohn's disease) and may be associated with infection with carcinogenic types of HPV.[187] There are reports of an increased frequency of anogenital warts in immunocompromised patients.[191] 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.

4.6. JC virus

ECCO Statement OI 4F
Progressive multifocal leukoencephalopathy (PML) is caused by reactivation of JC viral infection, which is latently present in 60–80% of adult Europeans. Specific screening recommendations for the risk of PML cannot be issued at present, but prescribing physicians should be aware of the disease [EL5, RG D]

ECCO Statement OI 4G
Patients with profound medical immuno-suppression, specifically those with anti α4 integrin therapy, and with new onset neurological symptoms should receive a contrast enhanced MRI of the brain and lumbar puncture for CSF analysis of JC viral load to detect PML [EL5, RG D]

4.6.1. Background

Progressive multifocal leukoencephalopathy (PML), is a rare but usually fatal opportunistic brain infection caused by reactivation of latent JC (polyoma) virus infection, that has become more common in the HIV/AIDS pandemic. Polyoma virus infection is ubiquitous in Europe, most commonly at young age and usually remains dormant for life. When three cases of PML in patients with multiple sclerosis (MS) and Crohn's disease (CD) were linked to treatment with the anti-α4 integrin antibody natalizumab, the commercial and investigational use of leucocyte trafficking inhibitors directed at α4 integrins was suspended (February 2005). Natalizumab therapy was subsequently resumed for multiple sclerosis[192–194] and for CD in the US, but it has as yet been denied a European licence for CD. An FDA warning (2008) about an increased risk of PML among patients treated with monoclonal anti-CD20 antibodies was issued after two patients with systemic lupus erythematosus treated with rituximab died of PML, illustrating the necessity of increased vigilance for other therapeutic antibodies.[195,196]

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

Reactivation of JC virus in the brain results in demyelination, giant astrocytosis and destruction of glial cells. PML is clearly associated with profound immune suppression such as AIDS, organ transplantation and haematological malignancy.

4.6.3. Preventive measures

Because of the risk of PML, natalizumab is available for MS only through a restricted distribution programme called theTOUCH™PrescribingProgram (see: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01380.html, http://www.emea.europa.eu/humandocs/Humans/EPAR/tysabri/tysabri.htm; http://www.fda.gov/bbs/topics/NEWS/2008/NEW01775.html,). A similar programme has become available for CD in the US, restricting its use to patients who have refractory disease after failing both immunomodulators and anti-TNF agents. Withdrawal of other immunomodulators, screening for and subsequent monitoring JC virus infection is mandatory. There have now been >20 000 patient-treatment years and (as of Q1 2009), at least two further cases of PML associated with natalizumab have been reported. The risk for individuals during extended treatment (>2 years) remains to be established.

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

Anti-adhesion molecule therapy offer major promise for the prevention of relapse of MS and CD, but the currently estimated 1/1500 risk of PML in patients exposed to natalizumab and the lack of adequate therapy for PML, calls for reliable screening strategies.[197,198] Nevertheless, whether JC viral load assessments in blood, urine, or cerebrospinal fluid (CSF) can predict the risk of PML is debated and needs further study. Patients with medically-induced immunosuppression, specifically with anti-integrin therapy, should be closely monitored for new neurological symptoms such as lethargy or personality change, and the appearance of neurological signs should prompt a contrast-enhanced cranial MRI and referral to an infectious disease specialist or neurologist for consideration of lumbar puncture to assess CSF JC viral load.

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4.6.5. Infection occurring during immunomodulator therapy

No single therapy has demonstrated efficacy for the treatment of PML as a consequence of JC virus reactivation in the brain. Controlled clinical trials with antiviral or cytotoxic agents including interferon-a2b, cytarabine, cidofovir and topotecan have been negative.[199] Since PML almost exclusively occurs in immunocompromised patients, any effort to overcome the immunosuppression should be considered. Immunomodulators should be discontinued immediately. Expert opinion from a neurologist or infectious disease specialist experienced in the management of patients with PML should be sought. Case reports, including a patient with multiple sclerosis treated with natalizumab, have suggested benefit of cytarabine for five days.[193,200] For patients with inflammatory forms of PML identified by MRI and neurologic deterioration, high dose intravenous glucocorticosteroids may be considered to decrease cerebral oedema, although steroids will increase immunosuppression.

4.7. Influenza virus

ECCO Statement OI 4H
Patients on immunomodulator therapy are considered to carry an enhanced risk for the development of influenza infections [EL4, RG C]

ECCO Statement OI 4I
An effective strategy to prevent influenza infections consists of annual vaccination with trivalent inactivated influenza vaccine [EL1a, RG A]. Routine influenza vaccination of all patients with inflammatory bowel disease on immunomodulators is recommended [EL2, RG B]. The live attenuated vaccine is not recommended. Vaccination appears not to have an impact on the activity of inflammatory bowel disease [EL4, RG D]. Seroconversion after influenza vaccine is not reduced by corticosteroids, methotrexate or anti-TNF therapy, nor by dual therapy with these agents, so monitoring the serological response is not warranted [EL2a, RG B]. Thiopurines or ciclosporin reduce influenza vaccine seroconversion rates [EL2a, RG B]

ECCO Statement OI 4J
Antiviral treatment in patients diagnosed early with influenza during an epidemic should be considered. Prophylaxis should follow national guidelines [EL5, RG D]

4.7.1. Background

There are two types of influenza virus that cause human epidemics: type A and type B. Influenza virus A is divided into subtypes, of which H1N1 and H3N2 are circulating globally.[201] Infection with influenza is associated with mortality, depending on risk stratification.[202]

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

No data exist on the incidence of influenza infection in patients with IBD, but immunomodulator therapy is generally considered to enhance the risk of influenza infection.[201]

4.7.3. Preventive measures

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 and Prevention.[201] Two types of vaccines are available. Live attenuated influenza vaccine (LAIV) should only be used for healthy persons age 5–49 years, so 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.[201] Little is known about the adaptive immune response to influenza vaccination in IBD patients, whether or not on immunomodulators. In organ transplant patients, several studies have shown that immunomodulators diminish antibody development to influenza vaccination, sometimes necessitating a two-dose vaccination regimen.[203–209] In patients with rheumatoid arthritis, anti-TNFα treatment has been reported to reduce antibody titres after influenza vaccination. A pediatric study in IBD showed a similar reduction of protective antibody development to influenza vaccination in patients on immunomodulators, without any influence on the activity of IBD. [210] However, the immune response remains sufficient to warrant annual influenza vaccination.[211–213] Based on risk stratification for influenza infection, IBD patients on immunomodulators are considered to be at risk and best receive annual TIV vaccination.[117] This preventive strategy is uncommonly applied in IBD patients and proof of benefit is circumstantial.[214–216]

Chemoprophylaxis

The drugs oseltamivir and amantadine both decrease the risk of symptomatic infection, when given in the early phase after contact with a patient with influenza. When given to a people in an institution during an outbreak, it reduced the extent and severity of the outbreak.[217] Post-exposure prophylaxis for household contacts is recommended in Sweden and Germany.[218]

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

Diagnostic approach and screening

Influenza is characterised by the sudden onset of fever with subsequent tracheobronchitis, although any upper respiratory infection syndrome can occur. In most cases, the diagnosis is based upon symptoms. Diagnostic tests for influenza include viral culture, serology, rapid antigen testing, reverse

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Table 2 Reports of parasitic infection.

Pathogen	*n*	Single, double, triple IMs	Anti-TNF related	CsA related	Deaths	References
Strongyloides stercoralis	3	S = 2 D = 1	1/3	0/3	1 out of 3 outcomes	225
Toxoplasma gondii	5	Unknown	5/5	0/5	Unknown	221

Legend: Single, double or triple IMs = concomitant therapy with one (S), two (D), or three (T) immunomodulators. CsA: ciclosporin.

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.

Treatment of the 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 rarely appropriate. 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.[219,220] 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.[218]

4.7.5. Infection occurring during immunomodulator therapy

Management of immunomodulator therapy

No data are available on the use of antiviral drugs for chemoprophylaxis or treatment of active influenza infection in patients with IBD, whether or not on immunomodulators. It seems advisable for immunocompromised patients to start antiviral therapy within 36 h of illness in the event of active influenza infection during an epidemic, in order to reduce risk of influenza-related complications.[201]

5. Parasitic and fungal infection

5.1. Background

ECCO Statement OI 5A
The risk of parasitic or fungal infection in inflammatory bowel disease has not been quantified. Systemic infections are exceptional, but mortality appears to be high [EL4, RG D]

Parasitic or fungal infections, like other opportunistic infections, are a consequence of a generic rather than disease- or therapy-specific risk among immunocompromised individuals. As a consequence, recommendations are empirical, based on first principles, or clinical judgement rather than a sound evidence-base. The infections considered in this section are the parasites *Toxoplasma gondii* and *Strongyloides stercoralis*, and fungal infections with *Aspergillus* spp., *Candida* spp., *Cryptococcus neoformans*, *Histoplasma capsulatum* and *P. jiroveci* (formerly *P. carinii*). The results of the systematic literature search are shown in Tables 2 and 3. Most sources are case reports, with substantial reporting bias relating to immunomodulator or biological therapy used to treat IBD or rheumatoid arthritis. Reports are skewed by one paper on granulomatous infectious disease associated with anti-TNF therapy. This study used the Adverse Event Reporting System (AERS), which is a passive reporting system that documents adverse reactions to medications in the US. The difficulty with

Table 3 Reports of fungal infection.

Pathogen	*n*	Single, double or triple IMs	Anti-TNF related	CsA related	Deaths	References
Aspergillus spp	33	S=6 D or T=27	31/33	4/33	5 out of 6 outcomes 27 outcomes unknown	226 221 227
Candida spp	89	S, D or T therapy unclear	65/89	0/89	Nil deaths reported but 38 outcomes unknown	13,221,228, 229
Cryptococcus neoformans	17	S=4 D or T=12 Unknown=1	14/17	0/17	1 out of 5 known outcomes 12 outcomes unknown	221,230–234
Histoplasma capsulatum	57	S or D or T therapy unclear	57/57	0/57	3 out of 18 outcomes 39 unknown outcomes	2,13,221,235–238
Pneumocystis jiroveci (*P. carinii*)	139	S, D, T therapy unclear	119/139	4/139	2 of 5 known outcomes 134 unknown outcomes	227,228,239–245

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the data is that there is no denominator, so the incidence of infection is unknown. Furthermore, it does not report outcomes.[221] Two additional studies report *P. jiroveci* after infliximab therapy. The first is a review of 84 cases of *P. jiroveci* with data gleaned from AERS between 1998 and 2003 for patients with rheumatoid arthritis being treated with infliximab. There are no denominators and no outcome data.[222] The second is a Japanese study[223] reporting on 5000 patients receiving infliximab for rheumatoid arthritis. The incidence of *P. jiroveci* in this population was 0.4%. Once again, there are no outcome data.

As a consequence, the risk of parasitic and fungal infections in inflammatory bowel disease cannot currently be quantified. A report of 1169 patients who had all received an anti-TNF therapy (GAIN (n=315) and CHARM (854)), identified opportunistic infections in 2.4% of 1169 patients, with all but one infection being non-systemic candidiasis.[224]

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

Corticosteroids, ciclosporin, tacrolimus, mycophenolate mofetil and anti-TNF therapy are. potent inhibitors of microbial specific T cell function, potentiating opportunistic infection with fungal species, *S. stercoralis* and a variety of intracellular pathogens. Immunosuppression not only reduces the threshold for infection, but also promotes dissemination and may induce pyrogenic or other systemic physiological responses. 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.

Consequently a high index of suspicion should accompany any complaint of breathlessness, cough, or confusion in a patient being treated with immunomodulators, with a low threshold for performing a chest radiograph, CT scan or MRI and lumbar puncture with specific diagnostic tests as appropriate (Section 5.4, Table 5). 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. Early implementation of therapy (such as parenteral ivermectin for disseminated strongyloidiasis) can be life-saving. Diagnostic delays usually reflect the failure to consider the possibility of systemic opportunistic infection when signs are few in the early stages.

5.3. Preventive measures

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

ECCO Statement OI 5B
No vaccines exist for preventing fungal infection. Environmental exposure should be avoided. Primary chemoprophylaxis is currently not indicated. Secondary chemoprophylaxis should be discussed with an appropriate specialist [EL5, RG D]

Fungi are found in soil or farm dust. Some appear ubiquitous (*Aspergillus* spp., *Candida* spp.), while others are associated with animals (*C. neoformans* in pigeon droppings) and some, such as *H. capsulatum*, are geographically distributed in the southern United States or Central Africa. Parasites are more commonly associated with endemic areas and gastroenterologists should be aware of travel to, or from, the tropics and the sub-tropics, where *S. stercoralis* is patchily endemic. There are, however, no vaccines for fungal or parasitic infections, so preventive measures depend on making immunocompromised individuals aware of the risks when travelling to endemic areas. General advice includes avoiding farms, pigeon lofts, or an extended duration of stay. This is, of course, not always possible, so a high index of suspicion is appropriate when treating patients, either inhabitants or travellers, from such areas. It is worth considering that it may be inappropriate to translate Western thresholds for treatment of IBD with immunomodulators to residents of endemic areas.

5.3.2. Immunisation and chemoprophylaxis for *P. jiroveci*

ECCO Statement OI 5C
No vaccines exist for preventing *P. jiroveci* pneumonia. For those patients on triple immunomodulators with one of these being a calcineurin inhibitor or anti-TNF therapy, standard prophylaxis with co-trimoxazole is recommended if tolerated [EL4, RG D]. For those on double immunomodulators, with one of these being a calcineurin inhibitor or anti-TNF therapy, a Consensus could not be reached on the use of prophylactic co-trimoxazole

There is no consistency in the approach to prophylaxis against *P. jiroveci* in patients with IBD treated with immunomodulators, despite some suggested guidelines.[246] That heavily immunosuppressed patients are at risk from *P. jiroveci* is not in doubt, but most patients with IBD treated with calcineurin inhibitors or infliximab are generally well nourished, on concomitant immunomodulators for a relatively short duration and are as much at risk from other opportunistic infections. This is unlike patients with HIV or those on immunomodulators after transplant surgery. A surrogate marker of severe immunosuppression in IBD patients is lacking. Since neither the necessity nor benefit has been established in IBD patients, recommendations from the Consensus are based on expert opinion and experience from other immunocompromised patients. A recent meta analysis showed a 91% reduction of occurrence of PCP when chemoprophylaxis with cotrimoxazole was administered in patients with haemotological cancers or transplants.[247] Patients with HIV disease and a CD4+ count $<$200/mL had fewer infections with *P. jiroveci* when maintained on cotrimoxazole.[248] It is rare for patients to acquire *P. jiroveci* when the CD4+ count is $>$200/mL. In another patient population, 13 cases of PCP were diagnosed among 519 patients undergoing allogeneic haematopoietic stem cell transplantation. Three of these were on prophylaxis, but these patients had a very low CD4+ count (median 131/μL).[249]

Consequently the Consensus took into account the simplicity and general lack of toxicity of chemoprophylaxis with

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Table 4 Results of Consensus voting on indications for *P jiroveci* prophylaxis.

Clinical situation	Recommendation for primary prophylaxis (Yes/total voters)
Prednisolone >20 mg/day for over 3 months	4/22 (all 4 were infectious disease specialists)
Prednisolone >20 mg/day with azathioprine/mercaptopurine or methotrexate	4/22 (all 4 were infectious disease specialists)
Any immunomodulator with ciclosporin or infliximab	14/22
Triple immunosuppression	22/22

cotrimoxazole along with the high mortality of active infection. Combinations of immunomodulators were considered particularly important. Participants were asked to vote (Yes or No, Y/N) on whether they would advise primary prophylaxis for patients on immunomodulator therapy. Table 4 displays the results of voting about prophylaxis for *P. jiroveci* by the Consensus. The infectious disease specialists were unanimous in recommending prophylaxis for patients with single, let alone double immunosuppression. This no doubt reflects their experience on the consequences and difficulty in treating *P. jiroveci*, which gastroenterologists see exceptionally rarely. In contrast, the views of the gastroenterologists no doubt reflect their experience on the frequent use of such agents without any opportunistic infection, let alone infection with *P. jiroveci*. It is for this reason that the votes are reported, since they illustrate contrasting views. More research is urgently needed to identifying immune parameters for defining at-risk patients.

There are multiple regimen for primary chemoprophylaxis: Trimethoprim–sulphamethoxazole (TMP-SMZ) is the prophylactic agent of choice with one one-strength tablet daily (80–400 mg) or half-dose daily of a double strength tablet (160–800 mg) or a double-strength tablet 3 times per week.

General measures to prevent infection may well be as important as chemoprophylaxis. These include the nutritional state of the patient, dose, duration and combination of immunomodulator therapy. In one 7 year follow up study of patients treated with ciclosporin, 3/86 patients (3.5%) died of opportunistic infections, but only 1 from *P. jiroveci* and 2 of *Aspergillus fumigatus* pneumonia. Some of these were treated with ciclosporin 8 mg/kg/day for up to 12 months.[227] In another 7 year follow up study there were no cases of *P. jiroveci* in 72 patients without chemoprophylaxis when the ciclosporin dose was limited to 5 mg/kg/day to achieve serum concentrations of 200–400 ng/mL, as well as limiting the duration to 3–6 months and introducing azathioprine in the last 4 weeks of steroid and ciclosporin therapy.[250]

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

5.4.1. Diagnostic approach and screening

ECCO Statement OI 5D
Screening for parasitic or fungal infection prior to immunomodulator therapy is generally considered unnecessary [EL5, RG D]. Specialist advice is appropriate for patients returning from endemic areas

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*, however, screening of patients with risk factors is best performed, although no method is ideal. Risk factors include sustained travel to, or residence in, endemic areas such as the tropics, or the Appalachians in the US (see also Section 8.6). Serologic testing is widely available and sensitive, but not specific. Relying on stool studies alone is inadequate and skin testing is experimental. Positive serology in a patient with a compatible clinical history preparing to undergo steroid therapy may be considered sufficient grounds for therapy (with an imidazole drug or ivermectin). Specialist advice should be sought.

ECCO Statement OI 5E
Clinicians should be alert to the possibility of parasitic or fungal infections in patients with inflammatory bowel disease who have unexplained symptoms, including fever, dyspnoea, or confusion and who are generally immunocompromised [EL5, RG D]

5.4.2. Interpretation of diagnostic tests for non-specialists

Specialist advice is recommended on the approach and interpretation of diagnostic tests. The succinct details below and Table 5 are intended as a general guide for non-specialists.

S. stercoralis

Microscopic identification of larvae in stool or duodenal fluid is the usual method of detection, but repeated samples may be required due to poor sensitivity. Larvae may be detected in sputum from patients with disseminated strongyloidiasis. Serology is indicated when the organism cannot be demonstrated by direct microscopy. Immunocompromised persons with disseminated strongyloidiasis usually have detectable IgG antibodies. Cross-reactions in patients with filariasis and other nematode infections may occur, so a positive test warrants continuing efforts to establish a parasitological diagnosis.

T. gondii

Detection of Toxoplasma-specific antibodies is the primary diagnostic method for a recent infection by *T. gondii*. Initially, test for Toxoplasma-specific IgG antibodies. A positive Toxoplasma-specific IgG titre indicates infection with the organism at some time. A negative IgM titre usually excludes recent infection, but a positive IgM titre is difficult to interpret because IgM antibodies may be detectable for as long as

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Table 5 Summary of diagnostic approaches to parasitic and fungal infections.

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

18 months after acute infection.The most common clinical presentation of *T. gondii* infection among patients immunocompromised patients is a focal encephalitis. Patients with *T. gondii* encephalitis are almost uniformly seropositive for anti-toxoplasma IgG antibodies. Anti-toxoplasma IgM antibodies are usually absent. Definitive diagnosis of *T. gondii* encephalitis (TE) requires a compatible clinical syndrome; identification of one or more mass lesions by CT or MRI; and detection of the organism in a clinical sample. For TE, this requires a brain biopsy, which is most commonly performed by a stereotactic CT-guided needle biopsy. Most clinicians rely initially on an empiric diagnosis, which can be established as an objective response, on the basis of clinical and radiographic improvement, to specific anti-*T. gondii* therapy in the absence of a likely alternative diagnosis. Brain biopsy is reserved for patients failing to respond to specific therapy.

Candida spp

The predominant organism is *C. albicans* (>60%) but there is a trend towards non-albicans (*C. glabrata*, *C. tropicalis*, *C. parapsilosis*). There are multiple direct and indirect methods of diagnosing *Candida* infection. A positive culture from a normally sterile body site is the gold standard. Cultures from blood, CSF, joint aspirate or other sterile surgical sites are generally diagnostic. *Candida* species will grow in standard blood culture bottles. Culture from most other sites cannot differentiate colonisation from infection, so must be interpreted in the clinical context. PCR and non-culture-based detection methods are being investigated but have not reached clinical use.

Aspergillus spp

Diagnosis is difficult, especially in the immunocompromised. Bronchoalveolar lavage (BAL) is only 50% sensitive and a definitive diagnosis may require invasive procedures or biopsy. Infiltrates on chest CT or a 'halo' sign in the correct clinical context is enough to commence therapy.

Non-culture based procedures include antigen or DNA detection. Serum ELISA detecting galactomannan is FDA-approved. Two positive ELISAs plus radiology plus clinical scenario is interpreted as 'probable invasive aspergillosis'. Microbiological or histopathological demonstration of fungal elements in body tissue or fluid **is ideal**, but not all branching fungi are *Aspergillus* spp., so other moulds need to be considered.

Histoplasma capsulatum

Most infections are identified as incidental findings on a chest radiograph but this fungus can disseminate. Diagnosis is made by culture, fungal stains of body fluids or tissues, or tests for antibodies or antigens. Culture is frequently negative in mild cases. Histopathology is rapid, but only 50% sensitive. Only a few yeast-forms may be present and can be misidentified as other fungi, such as *Candida* spp., *Penicillium* sp., or *Pneumocystis* sp.

Antibodies are detectable in 90% of patients after 2-6 weeks, but may not be present in immunosuppressed patients. A polysaccharide antigen is generally detectable in body fluids such as urine, CSF, or BAL fluid. It is detectable earlier than antibody serology or culture and has the potential to monitor therapy.

C. neoformans

Laboratory diagnosis is established by the isolation of the organism in culture, histopathology, or detection of a

Table 6 General guidance for treating parasitic or fungal infections.

Pathogen	Preferred regimen	Second-line	Duration
Pneumocystis jiroveci	Co-trimoxazole (trimethoprim + sulphamethoxazole)	Pentamidine	14–21 days
Strongyloides stercoralis	Ivermectin	Albendazole	2–3 days
Toxoplasma gondii	Sulphadiazine and pyrimethamine	Clindamycin plus pyrimethamine	21–28 days
Invasive *Candida albicans*	Fluconazole	Caspofungin	At least 14 days
Invasive *Aspergillus* sp.	Voriconazole	Amphotericin B deoxycholate	Until resolution of symptoms
Histoplasma capsulatum	Amphotericin B liposomal (Ambisome) then Itraconazole	Amphotericin B deoxycholate	2–3 months
Cryptococcus neoformans	Amphotericin B deoxycholate plus 5-flucytosine	Fluconazole	6–10 weeks

Specialist advice is necessary, since dose and duration of therapy depend on precise circumstances.

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polysaccharide capsular antigen. Analysis of CSF usually reveals a low white cell count with a normal or low-CSF glucose concentration and a positive cryptococcal antigen test. Cryptococcal antigen in the CSF (detected by latex agglutination) is very reliable and may also be positive in plasma. The cryptococcal antigen detection test is not useful for monitoring the course of therapy.

P. jiroveci (*P. carinii*)

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. Occasionally transbronchial or open lung biopsy is necessary. *P. jiroveci* trophozoites and cysts can be identified by light microscopy. Increasingly, immunofluorescence tests are used.

Molecular techniques, including polymerase chain reaction, have a high sensitivity and specificity but are not yet commercially available.

5.4.3. Treatment of the infection

ECCO Statement OI 5F
Specialist advice is appropriate for treating systemic parasitic or fungal infections [EL5, RG D].

Parasitic and fungal infections are uncommon and individual circumstances such as the level of diagnostic confidence, degree of immunosuppression, comorbidity and concomitant therapy make therapeutic decisions complex. Consequently treatment should be initiated and monitored and secondary chemoprophylaxis considered if immunomodulator therapy is re-introduced following specialist advice. General guidance for treatment is shown in Table 6, followed by more specific information, but specialist advice should be sought when treating these unusual infections.

P. jiroveci

Prophylaxis regimen: Co-trimoxazole (trimethoprim + sulphamethoxazole), double strength, 1 tablet three times a week.

Preferred treatment regimen: Co-trimoxazole (trimethoprim + sulphamethoxazole) for about 3 weeks. Cautions: sulphonamide may cause marrow suppression or renal impairment requiring dose adjustment or alternative therapy.

Second line treatment: Intravenous pentamidine for hospitalised patients, but may cause hyper- or hypotension, hyper- or hypoglycaemia, pancreatitis, renal impairment and numerous drug interactions. Clindamycin with primaquine is an alternative for outpatients.

S. stercoralis

Prophylaxis regimen: for patients exposed in an endemic area who are serology positive, take specialist advice.

Preferred treatment regimen: Ivermectin. Cautions: may exacerbate asthma, or cause rash or fever.

Second line treatment: Albendazole, but may cause hepatic impairment or marrow suppression.

T. gondii

Preferred treatment regimen: Sulphadiazine and pyrimethamine, after a loading dose of pyrimethamine, for about 3 weeks. Give folinic acid. Cautions: sulpha allergy, marrow suppression.

Second line treatment: Clindamycin with pyrimethamine and folinic acid.

Invasive candidiasis

Preferred treatment regimen (if *C. albicans*): Fluconazole (if no previous use of fluconazole) for at least 2 weeks after last positive blood culture, or the symptoms and signs have resolved (if not candidaemic). Cautions: hepatic impairment; clearance reduced in renal impairment.

Preferred treatment regimen (if not *C. albicans*): Intravenous amphotericin B deoxycholate for at least 14 days after the last positive blood culture, or the symptoms and signs have resolved (if not candidaemic). Cautions: renal impairment, hypokalaemia, hypersensitivity reactions.

Second line treatment: Caspofungin intravenously for at least 14 days after last positive blood culture or the symptoms and signs have resolved, ambisome, or abelcet.

Invasive aspergillosis

Preferred treatment regimen: Voriconazole until resolution of symptoms and signs.

Second line treatment: Intravenous amphotericin B deoxycholate until resolution of symptoms and signs. Cautions: Renal impairment; hypokalaemia; hypersensitivity reactions. Alternatives: Ambisome or abelcet.

H. capsulatum

Preferred treatment regimen: Intravenous amphotericin B liposomal (Ambisome) for about 3 weeks, followed by itraconazole for 2–3 months. Cautions: renal impairment, hypokalaemia, hepatic impairment, drug interactions. Measure itraconazole concentration.

Second line treatment: Amphotericin B deoxycholate followed by itraconazole, or ketoconazole for 3–6 months for mild disease.

C. neoformans

Preferred treatment regimen: Intravenous amphotericin B deoxycholate plus 5-flucytosine for 6–10 weeks. Can use ambisome or abelcet as alternatives to deoxycholate form of amphotericin. Cautions: renal impairment, hypokalaemia, infusion reactions, marrow suppression.

Second line treatment: Amphotericin B lisomal (Ambisome) plus 5-flucytosine, followed by fluconazole. If no CNS involvement, fluconazole alone for 3 months may be sufficient.

5.5. Infection occurring during immunomodulator therapy

ECCO Statement OI 5G
Starting or continuing immunomodulator therapy during treatment of parasitic or fungal infection depends on individual circumstances [EL5, RG D]. Reintroduction of immunomodulators after treatment is possible, in conjunction with secondary chemoprophylaxis. Specialist advice is appropriate

In the event of 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

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infection arises as a consequence or in association with immunosuppression, then it is unwise to reintroduce such therapy in that patient unless all other options are considered. None of the case reports, describe reintroduction of therapy after effective treatment of systemic parasitic or fungal infection. If a decision is made to re-introduce 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. This takes into account the treatment options available for the IBD, the general condition and wishes of the patient.

6. Tuberculosis

6.1. Background

Tuberculosis (TB) and malaria are the most common serious chronic infectious diseases in the world. The incidence of tuberculosis is increasing at the start of the third millennium, with the appearance of multiresistant (MDR-TB) and extremely resistant (XDR-TB) *Mycobacterium tuberculosis*. The worldwide incidence of TB in 2005 was 79/100,000 inhabitants. In contrast, the incidence of TB in 1997 was estimated by the World Health Organisation (WHO) at 10–24/100,000 inhabitants in most European countries, but higher (50–99/100,000) in some Southern and Eastern European countries. Although the incidence, prevalence and mortality of TB have decreased in Europe, it remains a global burden. The infection is more prevalent in developing countries, but migration, together with the HIV pandemic (an important reservoir for TB) have increased concerns of TB in economically-developed areas.[251,252] In the pre-infliximab era, people with IBD appeared to be at higher risk of TB than the general population. Immunomodulators appear to be the main reason for this increased risk.[253]

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

Anti-TNF therapy further increases the risk of TB infection. When TB occurs in patients on anti-TNF therapy, it is more commonly atypical (extrapulmonary in >50%, disseminated in 25% of cases), making the diagnosis more difficult. Mortality in patients with TB during anti-TNF therapy has been reported to be up to 13%.[254–258]

6.3. Preventive measures

ECCO Statement OI 6A
Patients diagnosed with latent TB should be treated with a complete therapeutic regimen for latent TB [EL1b, RG A]

ECCO Statement OI 6B
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 after specialist advice [EL5, RG D]

ECCO Statement OI 6cC
Chemotherapy for latent TB may vary according to geographic areas or patient's epidemiological background [EL5, RG D]. Specialist advice is appropriate

6.3.1. Impact of preventive actions

Preventive actions (meaning an active search for latent TB by chest X-ray, tuberculin skin testing, or gamma interferon assays) have a beneficial impact on the incidence of overt TB during anti-TNF therapy. Carmona and colleagues compared the rates of overt TB among patients with rheumatic diseases from the Spanish Society of Rheumatology Database on Biologic Products (BIOBADASER). Patients had a 21-fold higher risk of overt TB compared to the background Spanish population before preventive actions were proposed. The incidence of TB decreased by 78% after the adoption of official recommendations (Section 6.4.1). In a post-marketing surveillance of IFX among 5000 Japanese patients with rheumatoid arthritis, Takeuchi and co-workers confirmed that chemoprophylaxis decreased the number of cases with overt TB.[223,259]

6.3.2. Chemoprophylaxis

TB chemoprophylaxis regimens principally include options based on isoniazid (INH) for 6–9 months.[259–263] Depending on the geographic area or patient's background, the possibility of TB infection from multidrug-resistant strains should be considered. A generally effective regimen of INH for 6 months does not always prevent infection, since TB has been reported in two rheumatologic patients on this regimen.[264,265] More aggressive chemoprophylaxis is appropriate for at risk patients, including those from sub-Saharan Africa.[260,266]

6.3.3. Concerns about hepatotoxicity

ECCO Statement OI 6D
In spite of the hepatotoxic potential of some commonly used drugs in IBD, there are no reports indicating increased risk for isoniazid hepatotoxicity [EL4, RG C], but biochemical monitoring is considered essential

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, so dose-modification will not prevent severe liver injury in established hepatotoxicity. 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. Minor transaminase elevations (<3-fold) are common (10–20%) during isoniazid therapy and of no consequence. Some authors recommend clinical, rather than routine biochemical monitoring, for patients on isoniazid treatment,

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but most advise monitoring liver function at intervals, with cessation or alteration of therapy if the transaminases exceed >3-fold elevation associated with hepatitis symptoms or jaundice, or >5-fold in the absence of symptoms.[259,267–271]

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

6.4.1. Diagnostic approach and screening

ECCO Statement OI 6E
Careful evaluation (including history of epidemiological risk factors, physical examination, chest X-ray and tuberculin skin test according to national guidelines) for latent TB before the use of anti-TNF therapy is mandatory [EL1b, RG A]. It should also be considered before corticosteroids or other immunomodulators in patients at high risk of TB. Interferon-gamma release assays (IGRA) are likely to complement the tuberculin skin test and are preferred in BCG vaccinated individuals if available [EL4, RG D]. The performance of a second tuberculin skin test may be considered in immunocompromised patients 1–8 weeks after a first negative tuberculin skin test, according to national guidelines [EL5, RG D]

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 and no radiological evidence of active TB. A positive Mantoux reaction for TST is defined by an induration diameter $\geq$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.[260,272–274] These recommendations apply particularly to anti-TNF therapy. Experience suggests that TB complicating treatment for IBD with corticosteroids or immunomodulators is extremely rare, although the increased risk in populations at high risk (elderly white males, alcohol abuse, patients from subcontinental Asia, or Africa) should still be considered.

6.4.2. Tuberculin test distortion by BCG and immunomodulator therapy

Diagnosis of latent TB by TST may be 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 >30 years of age, irrespective of age at vaccination or re-vaccination. TST may also be negative in patients on corticosteroids for >1 month, or thiopurines or methotrexate for >3 months. The 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 1–8 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.[263,271,275–277] Any TST >5 mm should be considered positive for latent TB.

6.4.3. Interferon γ assays

Two new techniques of interferon γ release assays (IGRA) that target two specific proteins of *M. tuberculosis* (ESAT-6 and CFP-10). These are not affected by BCG-vaccination or environmental mycobacterial exposure and are commercially available (ELISPOT and QuantiFERON®-TB). Multiple studies, especially in immunocompetent patients, have demonstrated that IGRA is more sensitive and specific than a standard TST. In immunocompromised patients, IGRA seems to be more sensitive and specific than a standard TST. Further studies are urgently needed.[278–288]

6.5. Infection occurring during immunomodulator therapy

6.5.1. Management of immunomodulator therapy

ECCO Statement OI 6F
TB must be excluded in the event of persistent fever or non-specific clinical deterioration during immunomodulator therapy. If TB is diagnosed, anti TB-therapy must be started, anti-TNF therapy must be stopped and can be resumed after two months if needed [EL4, RG D]. It appears that 5-ASA, azathioprine, methotrexate or steroids do not need to be discontinued, provided that multi drug resistant TB has been excluded [EL4, RG D]

In case of active TB, TB treatment should ideally be completed before starting biological therapy.

In the initial report of TB incidence during anti-TNF therapy, 57% of cases were extra pulmonary and mortality was 13%. TB should be excluded as a cause of deterioration during anti-TNF therapy even if the clinical features are not suggestive of TB.[256,263]

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 TB therapy should be supervised by a thoracic physician or infectious disease specialist. It has also been suggested that anti-TNF treatment is either best delayed until completion of an anti-tuberculosis treatment, or that it should be avoided until at least 2 months after TB treatment has begun.[289,290]

Although there are no data assessing the impact of thiopurine therapy on the risk of TB in patients also receiving anti-TNF therapy, results from a small case–control study in rheumatoid arthritis have shown that the incidence of TB among patients using corticosteroids and immunomodulators is not increased.[264] This suggests that these medications can

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be continued during treatment of TB, although larger studies are warranted.

7. Bacterial infection

7.1. *Streptococcus pneumoniae*

ECCO Statement OI 7A
Patients with inflammatory bowel disease on immunomodulators are considered to be at risk patients for pneumococcal infections [EL4, RG C]

ECCO Statement OI 7B
Preventive strategy consists of a pneumococcal vaccination and with a single revaccination 3–5 years if the patient is still immunocompromised [EL5, RG D]. Immunity to *S. pneumoniae* after polysaccharide vaccination is not affected by corticosteroids or anti-TNF therapy [EL2a, RG B], nor by azathioprine [EL2b, RG C]. Methotrexate treatment is associated with much lower pneumococcal vaccine-induced seroconversion [EL2a, RG B]

ECCO Statement OI 7C
Immunomodulator therapy should be temporarily withheld until the resolution of active infection [EL5, RG D]. Treatment of pneumonia in patients on immunomodulators must always cover *S. pneumoniae*

7.1.1. Background

S. pneumoniae is a Gram-positive facultative anaerobic coccus which may cause serious or lethal infections including pneumonia, sepsis, or meningitis.[291] IBD patients on immunomodulators are considered high-risk patients for invasive pneumococcal disease.[117,214] In cohort studies bacterial pneumonia is one of the most prevalent infections in IBD patients on immunomodulators.[26,292] Invasive infection with *S. pneumoniae* related to immunomodulators in IBD has been reported.[293] Current recommendations for the 23-valent pneumococcal vaccine include patients on immunomodulators.[216]

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

Host defences against *Streptococcus* spp. depend on both humoral and cellular immunity. Predisposing conditions to pneumococcal infection are numerous, including immunosuppression in about a third of all diagnosed cases.[294] We did not find studies relating specific drugs to risk, although cases have been described with several drugs, including anti-TNF therapy. Although the incidence seems to be increased in immunocompromised patients, we did not find studies documenting the degree of increased severity or worse outcomes in these patients.

7.1.3. Preventive measures

The 23-valent pneumococcal vaccine should ideally be administered before the start of immunomodulator therapy, since immunomodulators may reduce the antibody response to the vaccine. This has been shown in patients with rheumatic diseases.[291,295–299] Therefore, the vaccine is best administered at the time of IBD diagnosis, or at least two weeks before the start of immunomodulators.[291] Repeat vaccination is recommended after three to five years if the patient remains on immunomodulator therapy[117,291] (http://www.cdc.gov/mmwr/PDF/rr/rr4608.pdf).

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

Diagnostic approach and screening

The most frequent and severe manifestations of pneumococcal infection are pneumococcal pneumonia and pneumococcal meningitis (with or without pneumococcal bacteremia). For both conditions it is not possible to differentiate a pneumococcal aetiology from other bacterial causes on the basis of the history or clinical signs. Whenever possible, relevant clinical samples (blood, cerebrospinal fluid, good respiratory sample) should be taken, analysed and cultured upon presentation, but this should not delay treatment.

Treatment of the infection

Empirical treatment should be started immediately for either meningitis or pneumonia covering *S. pneumoniae* and other common bacterial causes. The choice of antibiotic should follow local guidelines based on local epidemiology, because penicillin susceptibility varies widely.[300,301]

7.1.5. Infection occurring during immunomodulator therapy

Management of immunomodulator therapy

Antibiotic treatment of pneumonia in patients with IBD should always cover *S. pneumoniae*. Penicillin is the standard antibiotic for penicillin-susceptible pneumonia and meningitis, but local advice on resistance is appropriate,[302] especially since their immunosuppression may be associated with an increased risk of penicillin resistance. In the event of invasive pneumococcal infection, immunomodulator therapy is best temporarily withheld until resolution of the infection.[26,293,303]

7.2. *Legionella pneumophila*

ECCO Statement OI 7D
Patients with inflammatory bowel disease on immunomodulator therapy with pneumonia should be tested for *L. pneumophila* [EL4, RG D]

ECCO Statement OI 7E
Immunomodulator therapy should temporarily be withheld until resolution of the active infection [EL5, RG D]

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7.2.1. Background

L. pneumophila is an aerobic Gram-negative coccobacillus causing pneumonia, which can be fatal.[304] The most common route of transmission is airborne and reservoirs include aquatic systems such as cooling towers, evaporative condensers, humidifiers and decorative fountains.[305]

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

Immunomodulator therapy is considered a high-risk condition for infection with *L. pneumophila*.[304] Invasive *L. pneumophila* infections, some with fatal outcome, related to immunomodulators for IBD or rheumatological patients have been reported.[306–311]

7.2.3. Preventive measures

No vaccine is available and effective chemoprophylaxis has not been described. Since most epidemics of *L. pneumophila* can be linked to water reservoirs, prophylactic measures include regular cleaning and maintenance of different water systems.[305]

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

Diagnostic approach and screening

Clinically and radiologically *Legionella pneumonia* cannot be distinguished from pneumococcal pneumonia. The key to diagnosis is appropriate microbiological culture, in association with real-time PCR if available. Serological testing and antigen detection in the urine are also available.[304]

Treatment of the infection

Treatment for *L. pneumophila* consists of macrolide or fluoroquinolone antibiotics. Empirical treatment of severe community-acquired pneumonia should always cover *L. pneumophila* especially in the immunocompromised.[300,301]

7.2.5. Infection occurring during immunomodulator therapy

Management of immunomodulator therapy

Curative treatment consists of macrolide or fluoroquinolone antibiotics.[304,309] Immunomodulator therapy is best temporarily withheld until resolution of the active infection, although recurrent infection has been reported, so careful consideration is necessary about the benefit of continuing immunomodulators.[309]

7.3. *Salmonella* species

ECCO Statement OI 7F
Patients receiving immunomodulators are at risk of more severe infections with *Salmonella enteritidis* and *S. typhimurium* [EL4, RG C]

ECCO Statement OI 7G
Prevention of *Salmonella* sp. infections consists of food hygiene (avoiding raw eggs, unpasteurized milk and insufficiently cooked or raw meat) [EL5, RG D]

ECCO Statement OI 7H
Immunomodulators should be temporarily withheld until resolution of the active infection [EL5, RG D]

7.3.1. Background

Salmonella is an aerobic Gram-negative bacillus causing enterocolitis or systemic infection. *S. enteritidis* and *S. typhimurium* are the most common serotypes.[312,313] Infection is typically acquired through consumption of contaminated food or water. Early infection starts within the gastrointestinal tract, but patients may present with symptoms of disseminated infection such as sepsis, meningitis, urinary tract infection, or reactive arthritis.[312]

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

Immunomodulator therapy is considered a high-risk predisposing condition for intestinal or systemic infections with *Salmonella* spp.[314] Invasive *Salmonella* spp infection, some with fatal outcome related to immunomodulator therapy for IBD or rheumatologic patients have been reported.[221,306,310,315–319]

7.3.3. Preventive measures

Prevention consists of food hygiene: advise immunocompromised patients to avoid the consumption of raw eggs (fresh mayonnaise), unpasteurised milk and undercooked or raw meat (including carpaccio).[312]

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

Diagnostic approach and screening

The diagnosis should always be considered in patients with fever. Definitive diagnosis of enteric fever is made by isolating *S. typhi* or other *Salmonella* sp. from blood, stool, or urine.

Treatment of the infection

Salmonellosis is treated with antibiotics such as fluoroquinolones or third-generation cephalosporins, depending on the local susceptibility pattern.

7.3.5. Infection occurring during immunomodulator therapy

Management of immunomodulator therapy

Empirical treatment for severe infections without a clear focus or suspicion of enteric fever should always cover *Salmonella* sp., using fluoroquinolones or cephalosporins. Curative treatment of confirmed Salmonellosis consists of fluoroquinolones or third-generation cephalosporins, depending on local susceptibility patterns.[302] Immunomodulator therapy is best temporarily withheld until resolution of the active infection, although recurrent infection and asymptomatic carriage can occur. Confirmation of clearance through stool culture in immunocompromised patients seems advisable.

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7.4. *Listeria monocytogenes*

ECCO Statement OI 7I
Patients receiving immunomodulators are at risk of systemic and central neurological infections with *L. monocytogenes* [EL4, RGC]. The incidence appears higher in patients treated with anti-TNF therapy compared to other immunomodulators

ECCO Statement OI 7J
Prevention includes avoidance of unpasteurized milk or cheese, uncooked meat and raw vegetables, especially during pregnancy [EL5, RG D]. Patients on anti-TNF therapy who present with meningitis or other neurological symptoms demand full attention and should be thoroughly investigated as soon as such symptoms develop [EL5, RG D]

ECCO Statement OI 7K
Anti-TNF therapy should be discontinued during infection. No Consensus was reached on whether anti-TNF therapy should not be re started

7.4.1. Background

L. monocytogenes is an aerobic Gram-positive and facultative intracellular bacillus.[320] It is an opportunistic food-borne pathogen which has the capacity to survive many food-processing procedures. *L. monocytogenes* can cause relatively mild gastroenteritis, but in IBD or rheumatologic patients on immunomodulator therapy, it may lead to systemic sepsis, meningoencephalitis, or rarely cholecystitis and arthritis.[221,306,310,317,321–326] The mortality rate of systemic infection is as high as 30%, even with antibiotic therapy.[327] Infection during pregnancy often leads to spontaneous abortion or stillbirth.[327]

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

Immunomodulator therapy is considered a high-risk predisposing condition for infections with *L. monocytogenes*.[327] Compared to other immunomodulator therapies, anti-TNFα treatment appears to carry a particular risk for serious infection with *L. monocytogenes*.[310,326]

7.4.3. Preventive measures

Prevention consists of food hygiene: avoid soft or unpasteurised cheese, unpasteurised milk, undercooked meat and raw vegetables.[326,327]

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

Diagnosis is made by appropriate microbiological culture and curative treatment consists of ampicillin, amoxicillin, or sulphamethoxazole/trimethoprim.[302]

7.4.5. Infection occurring during immunomodulator therapy

Management of immunomodulator therapy

Early infection starts within the gastrointestinal tract. A high index of suspicion in patients on immunomodulator therapy who present with signs of meningitis or other neurological symptoms is appropriate, with intensive investigation including lumbar puncture as soon as such symptoms develop.[326] When patients have meningoencephalitis without initial proof of *Listeriosis*, the pathogen should still be covered by the antibiotic regimen. No data are available on whether immunomodulators should be temporarily or indefinitely withheld in the event of active infection.

7.5. *Nocardia* species

ECCO Statement OI 7L
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, RG C]

ECCO Statement OI 7M
The prevention of *Nocardia* sp. infections consists of avoiding direct contact with soil or inhalation of soil contaminated dust [EL5, RG D]

ECCO Statement OI 7N
Anti-TNF therapy should be discontinued indefinitely in the event of infection with *Nocardia* sp. [EL5, RG D]

7.5.1. Background

Nocardia species are aerobic Gram-positive, weakly acid-fast actinomycetes. They are ubiquitous soil organisms, responsible for local skin infections through direct contact, or necrotising pulmonary infections through inhalation.[328] Haematogenous dissemination to the brain occurs in up to 33% of all cases, most of which occur in immunocompromised hosts.[328]

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

Nocardia species infection is increasingly found in the immunocompromised patient. People with IBD or rheumatologic disease on immunomodulator therapy are considered at risk. Reports of cutaneous, pulmonary, or neurologic *Nocardia* sp. infection in patients on anti-TNFα treatment or corticosteroids have been published.[221,310,329–331]

7.5.3. Preventive measures

The prevention of cutaneous *Nocardia* sp. infections consists of skin hygiene, avoiding soil-infected skin lesions and avoiding inhalation of soil-contaminated dust.[328]

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

Diagnostic approach and screening

Nocardia sp. can be diagnosed rapidly by examination of sputum, pleural, or bronchial lavage fluid by Gram stain and a modified acid-fast stain. Long-term culture up to six weeks is necessary to grow the pathogen.[328]

7.5.5. Infection occurring during immunomodulator therapy

Management of immunomodulator therapy

Treatment consists of sulphamethoxazole/trimethoprim and/or ceftriaxone. Antibiotics should be continued until the disappearance of all lesions, which can take several months.[328] All immunocompromised patients (regardless of the site of disease) 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.[294] In order to obtain complete resolution of the infection, case reports suggest that anti-TNFα treatment should be discontinued indefinitely.[329,330]

7.6. *Clostridium difficile*

7.6.1. Background

ECCO Statement OI 7O
The pattern, virulence and presentation of *C. difficile* are currently changing. Inflammatory bowel disease is an independent risk factor for infection with *C. difficile*. In inflammatory bowel disease *C. difficile* is mostly community-acquired. Patients with colitis are particularly susceptible. Concomitant diagnosis of inflammatory bowel disease and *C. difficile*-associated diarrhoea (CDAD) is a predictor of an increased need for hospitalisation and increased mortality [EL2, RG B]

The pathogenicity of *C. difficile* is dependent on toxin production. Two main toxins are secreted by the vegetative forms of the germ, toxins A (enterotoxin) and B (cytotoxin). *C. difficile*-associated disease (CDAD) typically presents with watery diarrhoea (at least five bowel movements of liquid or unformed stool during 36 h), malaise, abdominal pain, fever, or leukocytosis.[332,333]

A retrospective observational study at a US referral centre in 2007, reported a significant rise of *C. difficile* infections in IBD patients, from 1.8% in 2004 to 4.6% in 2005.[334] The adjusted odds ratio for the development of CDAD was 2.9 (95% CI 2.1–4.1) in IBD patients compared to non-IBD. The adjusted OR was 2.1 for CD (95% CI 1.3–3.4), 4.0 for UC (95% CI 2.4–6.6) and the diagnosis of IBD was an independent risk factor for CDAD.[335] A significant rise in hospitalisation for IBD complicated by *C. difficile* infections between 1998 and 2004 has been reported (24/1000 *vs* 39/1000 for UC, 8/1000 *vs* 12/1000 for CD), including prolongation of hospital stay and a four-fold increase in mortality.[336] Colectomy is necessary in a substantial number of patients.

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

Immunomodulators are a known risk factor for acquisition of *C. difficile* and development of CDAD. Experience from solid organ transplantation shows an increase in incidence and severity of CDAD after transplantation.[337] Immunosuppression may also be an independent risk factor for mortality in patients with CDAD.[338] Data regarding IBD patients, immunosuppression and CDAD remain sparse. In one study maintenance immunomodulators, but not biologic therapy, were independently associated with the emergence of CDAD in IBD.[334]

7.6.3. Preventive measures

ECCO Statement OI 7P
Chemoprophylaxis for CDAD is not warranted. Hygiene procedures in a nosocomial setting are recommended [EL2, RGB]. The safety and efficacy of probiotics remain to be established

Alcoholic hand rubs do not eliminate *C. difficile* spores. Furthermore, the presence of disinfectants can provoke sporulation. Mechanical elimination of spores by soap and handwashing is recommended.[339] Hypochlorite solutions (unbuffered or phosphate-buffered) have been shown to reduce *C difficile* contamination even in high touch areas (bed rails, switches, bed-side telephones, or call buttons).[340] Even though data from controlled trials are lacking, studies suggest a decrease in CDAD cases when bleach is used as a cleaning agent.[341,342] Patients diagnosed with, or strongly suspected with infection, should be placed in isolation (single rooms) or cohorted together. Care workers should wear disposable gowns and gloves when entering the patient's room.

Recurrent CDAD has been treated effectively by *Saccharomyces boulardii*, confirmed by meta-analysis.[343] On the other hand, methods and source data for this metaanalysis are disputable, so they do not provide sufficient evidence to recommend probiotics or prove their safety in the treatment of CDAD. Occasional cases of fungaemia in immunocompromised patients taking *S. boulardii* have been reported.

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

Diagnostic approach and screening

ECCO Statement OI 7Q
Screening for *C. difficile* is recommended at every flare in patients with colonic disease [EL3, RGD]. Tests for both cytotoxins A and B are recommended [EL2, RG B]

In routine clinical practice, several different laboratory tests can be used to diagnose *C. difficile* infection: toxin detection (93% laboratories in Europe, of which 79% use enzyme immunoassay for toxin A and/or toxin B and 17% use the tissue cytotoxicity assay for toxin B), culture of *C.*

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difficile (55% laboratories), glutamate dehydrogenase detection (6% laboratories) and PCR (2% laboratories).[344] *Enzyme immunoassays (EIA)*: detect the toxins (A and/or B) produced by toxigenic strains of *C. difficile*. There are numerous commercially available EIAs with different sensitivities and specificities (ranging from 63–99% and 75–100% respectively). Since development of CDAD does not depend on the presence of both toxins, while toxin A-negative *C. difficile* strains account for up to 3% of CDAD, EIAs designed to detect only toxin A are likely to underreport CDAD. Toxin A-specific EIAs were applied in 58% laboratories, surveyed in 2003.[345,346] although more now use EIAs designed to detect both toxin A and toxin B. *Culture of C difficile*: performed on selective agar (e.g. cycloserine, cefoxitim agar). Before innoculation with stool, an enrichment step can be performed by exposure to alcohol to select spore-forming bacteria. Incubation time is usually 48 h. *C. difficile* can then be identified by morphological criteria, characteristic odour and antigen-detection by latex agglutination. *Cytotoxicity assay*: for *C difficile* toxin B (TcdB). This still represents the diagnostic gold standard despite its long turnaround time (24–48 h).[347,348] It uses the cytopathic effect of toxin B on the cytoskeletal structure of mammalian cell culture lines, which can be abrogated by *C. difficile* or *C. sordelli* antitoxin. *PCR*: detection by amplifying the *tcdB* gene. Sensitivity and specificity for PCR were 87.1% and 96.5% respectively, compared to the cytotoxicity assay. Positive and negative predictive values were 60.0 and 99.2% respectively.[349] Real time PCR had a higherculture than EIAs. *Detection in IBD*: Between 5.5% and 19% stool samples are reported to be positive for *C. difficile* among IBD patients with a relapse.[350,351] Consequently, stool testing for *C. difficile* seems to have a high yield during flares of IBD and is generally considered appropriate. The endoscopic picture of *C. difficile*-associated disease usually shows diffuse or scattered erythema. Pseudomembranes are only rarely found and their absence does not exclude infection. For CDAD in IBD, no patient who was positive for *C. difficile* showed the pathognomonic pseudomembranes in endoscopy. In the general population, endoscopy has only limited sensitivity (50%) and cannot be recommended as a diagnostic tool for CDAD.[352]

Treatment of the infection

ECCO Statement OI 7R
Metronidazole and oral vancomycin are equally effective in treating mild to moderate CDAD [EL1, RG B]. 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, RGB] and is therefore preferable. In case of multiple recurrences, pulsed dosing of vancomycin is a reasonable treatment option and withdrawal of immunomodulators should be considered [EL2, RG B]

In a meta-analysis, antimicrobial exposure has been shown to be an independent risk factor for both *C. difficile* carriage (pooled OR = 4.2, 95% CI = 3.1–5.9) and CDAD (pooled OR = 5.9, 95% CI = 4.0–8.5) in the general population.[353] Almost all classes of antibiotics and broad spectrum antibiotics in particular are associated with CDAD, with the exception of aminoglycosides. Recent studies have emphasized the importance of fluoroquinolones, which seem to pose the greatest risk for the development of CDAD compared to other common antimicrobials.[354,355] The first step in the treatment of CDAD is withdrawal of antibiotics, a measure which leads to recovery in up to 25% of non-IBD patients with CDAD.[356,357] Data from IBD are lacking. Metronidazole is generally first line therapy for patients experiencing a first, or even a second episode of CDAD[358] although this depends on local susceptibility. The usual oral treatment regime is 200–250 mg four times daily or 400–500 mg three times daily for 10 to 14 days. The glycopeptide antibiotic vancomycin is highly effective for CDAD and preferable for multiple recurrences of CDAD, or if there is local resistance to metronidazole.[359] Vancomycin is not superior to metronidazole for the first or second episode of CDAD, but is more costly and runs the risk of promoting resistance among enterococci.[357,360] Nevertheless, for patients with symptoms of severe CDAD, or if the patient's condition fails to improve or deteriorates on metronidazole, then early use of vancomycin is recommended.[361] Signs of severe CDAD include a systemic inflammatory response (tachycardia, fever), electrolyte imbalance, volume depletion, hypotension, ileus, toxic megacolon or peritonitis. The dose of vancomycin for acute CDAD is 125 mg every 6 h, which is of equivalent efficacy to 500 mg four times daily.[362] To reduce the recurrence rate of CDAD, a tapered or pulsed treatment regimen with vancomycin has been proposed on the basis of significantly reduced relapse rates following pulsed schedules. A pulsed schedule means vancomycin 125–500 mg every three days for 2–3 weeks.[359] It is unexpected, but notable that reported recurrence rates in IBD patients with CDAD are low compared to the general population (0.1% *vs* 8.7%) which questions the necessity of a pulsed treatment approach.[335] More data are needed and much higher recurrence rates of CDAD have been reported.

7.6.5. Infection occurring during immunomodulator therapy

ECCO Statement OI 7S
In CDAD it remains to be established whether concomitant therapy with immunomodulators should be withheld [EL5, RG D]

There are insufficient data to recommend a strategy for managing CDAD in patients on immunomodulators. Azathioprine/6-mercaptopurine therapy, but not biological (anti-TNFα) therapy has been significantly associated with *C difficile* infection.[334] Up to 78% of IBD patients positive for *C difficile* in this study were reported to be taking immunomodulators or anti-TNFα therapy, but the study was not sufficiently powered

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to address attributable risk. Clearly the risk and benefit of immunomodulator therapy should be questioned in such patients, but it remains a matter of clinical judgement 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[363] so there seems no reason to avoid corticosteroids.

8. Special situations

8.1. Patients travelling frequently or to less economically developed countries

8.1.1. Guidelines for the IBD patient travelling to less economically developed countries

The traveller 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 with IBD medication, or lack of such medication due to bad planning or unexpected change in the travel itinerary
(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. The clinician should ensure that the traveller understands the risks involved from their proposed itinerary. The medical requirements of the patient and degree of immunocompromise should also be taken into consideration when planning the journey, to minimise medical risks during travel.

8.1.2. Pre-travel consultation

Pre-travel interventions should be evaluated for both safety and efficacy. For example, patients with IBD taking IMs should be discouraged from visiting South American or sub-Saharan African countries where yellow fever is endemic, or yellow fever vaccine (a live attenuated vaccine) is required. Furthermore, patients with IBD should ideally be provided with adequate medication, instructions for emergency self-treatment in the event of an exacerbation of their underlying disease in a remote location where medical assistance may not be readily available, and adequate health insurance which includes cover for evacuation by air.

Guidelines regarding which vaccinations to take and when, or what preventive measures or drugs to use when travelling to less economically developed countries are frequently updated by the Infectious Diseases Society of America.[364] Vaccine-preventable diseases include: hepatitis A, typhoid fever, yellow fever, Japanese B encephalitis, meningococcal meningitis, tick born encephalitis, poliomyelitis, influenza, mumps, measles, diphtheria, and tetanus. Malaria, traveller's diarrhoea, tuberculosis and insect-borne diseases 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?

ECCO Statement OI 8A
The clinical manifestations, complications and response to therapy of travel-associated diseases among travellers with inflammatory bowel disease are unknown. Infections with enteropathogenic microorganisms may cause reactivation of quiescent inflammatory bowel disease [EL4, RG C]. Patients with inflammatory bowel disease should have a pre-travel consultation. Travellers with inflammatory bowel disease should be aware of the balance of risks between immunomodulator therapy and travel related infections

The effect of travel-associated diseases on the clinical manifestations of IBD has never been studied. However, several epidemiological investigations indicate that infections with enteropathogens which might be acquired during travel, can both provoke the initial onset of IBD and are associated with reactivation of quiescent disease.[365] Powell and Wilmont showed in the 1960s that following epidemics of *Salmonella*, *Shigella*, or *Yersinia* sp., a small but reproducible percentage of patients develop typical IBD.[366] The onset of IBD has also been described following sporadic infection with enteropathogens.[367]

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

ECCO Statement OI 8B
The effect of immunomodulators on the onset and severity of preventable, travel-associated diseases in patients with inflammatory bowel disease is not fully known [EL5, RG D]

An extensive literature search yielded only scant case reports regarding the contraction of travel-associated or vaccine-preventable infections by immunocompromised patients. For example, steroid use was associated with fatal paralytic poliomyelitis in one patient following administration of live oral polio vaccination to his daughter. Six patients in south-east Asia developed malaria, one fatal, one asymptomatic, while taking steroids and other immunosuppressants. Malaria has also been reported in a patient receiving azathioprine and other immunosuppressive drugs after kidney transplantation. It is interesting that ciclosporin may have a protective influence, including an anti-parasitic effect in malaria and a possible decrease in HBV replication. Anti-TNF drugs have been associated with reactivation of HBV in some patients and malaria (in one patient).

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In most cases, the diseases did not behave differently and the drugs were not given as mono-therapy. Moreover, the disease for which the drug was administered was not IBD in most cases. Thus it is impossible to extrapolate the real effect of a single drug on the severity of these preventable diseases in patients with IBD.

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, given their altered immune status which predisposes them to infectious diseases and possible severe course of disease, once contracted.

Three main issues have to be addressed when considering vaccination of patients with IBD on immunomodulators:

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

Vaccination safety

Effect of vaccination on IBD: Many alterations in immune function have been described in patients with IBD and it is generally considered that an over-active adaptive immune system is driving the chronic inflammatory state in these patients. 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.[368]

ECCO Statement OI 8C
Immunisation before travel for patients with inflammatory bowel disease who are not on immunomodulators should follow standard guidelines for healthy travelers, according to travel destination [EL5, RG D]

Inactivated vaccines: There are few systematic data regarding the safety of vaccines in patients with IBD being treated with immunomodulators, so inference from immunosuppressed patients with other disorders is necessary. Killed, inactivated or recombinant vaccines have been administered to many patients with variable degrees of immunosuppression and IBD, as well as other disorders (transplantation, rheumatic disorders, and chronic pulmonary disease). Most studies have examined responses to DTP, Influenza, Pneumococcus or Hepatitis B vaccines. 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 for appropriate indications.[369–372]

ECCO Statement OI 8D
Vaccination is best given before immunomodulator therapy [EL 4, RG D]

ECCO Statement OI 8E
Non-live vaccines are generally considered safe in patients with inflammatory bowel disease regardless of immunomodulator therapy, but may be less effective. This includes — Diphtheria and tetanus toxoids, acellular pertussis, inactivated parenteral poliovirus vaccine, Influenza, Pneumococcal polysaccharide, recombinant Hepatitis B vaccines [EL2a, RGB], as well as Hepatitis A, parenteral Typhoid (*Salmonella typhi* Vi polysaccharide), Meningococcal polysaccharide, oral killed Cholera, inactivated Japanese encephalitis, Human papilloma virus and inactivated tick-borne encephalitis vaccines [EL4, RG C]

Live-attenuated vaccines, including family exposure: These are generally considered unsafe for immunosuppressed patients, due to concerns about the possibility of causing disease by the otherwise attenuated organism. For instance, a patient on long standing prednisolone treatment (12.5 mg/day) was reported to succumb to fatal paralytic poliomyelitis 2 months after his daughter received live oral polio vaccine.[373] However, live-poliomyelitis vaccine-associated disease has also been reported in persons with an intact immune system, so the implications of this case are difficult to interpret. Nevertheless, the CDC guide on contraindications to vaccination advise against administering live-attenuated vaccines to patients treated by long-term immunosuppressive therapy, including steroids. Such vaccines include Measles–Mumps–Rubella (MMR), Typhoid Ty21a, Vaccinia, Yellow fever, live-attenuated influenza vaccine (LAIV) and BCG, which are designated as contraindicated in such patients.[372] On the other hand, in a single retrospective observational study, 49 children with Juvenile Rheumatoid Arthritis received the MMR vaccine while being treated with methotrexate (MTX, mean dose 11 mg/m^2), some also being treated with prednisolone. None of the patients developed measles following the vaccination.[374] Moreover, MMR was administered safely to 31 pediatric patients after liver transplants under tacrolimus or ciclosporin.[375] The CDC does not take a position on the safety to the parent receiving immunomodulators whose child is vaccinated. This is not that uncommon in patients with IBD, when the mother or father of a baby due to have MMR may be receiving steroids, azathioprine or other IMs. However, no case of measles has been reported in such circumstances.

Varicella live virus vaccine is probably safe in patients who have stopped thiopurines or MTX for at least one week before and one week after vaccination although longer than a week's cessation of thiopurines or MTX may be desirable. However, the available data is derived from the pediatric population. In studies recently reviewed by the Canadian national advisory committee on vaccination over 1000 pediatric patients with acute lymphoblastic leukaemia (ALL) in remission received varricella vaccine. Many of these children were under maintenance therapy, which was withheld for 1 week before to 1 week after vaccination. Mild vaccine-related rash was seen in 40–50% of patients, and fever in 20%. Of patients who developed rash, 40% were

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treated by acyclovir, and no severe life-threatening adverse events were reported. Thus, varicella vaccine to ALL children was incorporated into clinical guidelines advocating withholding chemotherapy at least 1 week before to 1 week after vaccine.[376] However, there is no data to support the safety of this approach in immunosuppressed IBD patients.

Despite the lack of evidence, some expert opinion groups contend that live-virus vaccines can be given safely to children receiving prolonged prednisolone treatment at a dose (<2 mg/kg/day or <20 mg prednisone/day if weighing more than 10 kg), and also to children receiving higher doses for less than 14 days.[117,372]

ECCO Statement OI 8F
Live attenuated vaccines are contra-indicated in IBD patients on immunomodulator therapy (MMR, Typhoid Ty21a, Vaccinia, Yellow fever, live attenuated influenza vaccine, varicella, oral polio and BCG) [EL5, RG D]. Live-virus vaccines are probably safe in patients on less than 20 mg prednisone daily, or on higher doses provided they have been given for less than 14 days [EL5, RG D]

ECCO Statement OI 8G
It is generally recommended that administration of live attenuated vaccines should be avoided for at least 3 months after treatment with immunomodulators is stopped. This delay may be reduced to 1 month in case of use of corticosteroids alone. Immunomodulator therapy should also be withheld for at least 3 weeks from the time of a live vaccine injection [EL5, RGD]

Acquisition of adequate immunity [Vaccine response in patients on immunomodulators or biological therapy]

CD and UC patients have been reported to have a reduced humoral response to booster Tetanus immunisation, independent of steroid therapy.[377] The ability of immunosuppressed patients to acquire immunity to infectious agents following vaccination varies according to the type of vaccine and the specific immunosuppression regimen.

Influenza vaccine: Thus, in three controlled studies, patients with rheumatoid arthritis on anti-TNF therapy generated similar rates of protective antibodies to influenza vaccine, albeit at a lower mean titre, compared to patients not taking these drugs, or normal controls.[211–213] Similarly, patients with rheumatoid arthritis treated with MTX did not have reduced immunity after influenza vaccine immunisation.[211,213] In two controlled studies of lupus patients, azathioprine, but not prednisolone (10 mg), reduced seroconversion to influenza vaccine.[378,379] In another study of 59 renal transplant recipients, patients treated with azathioprine and prednisolone had similar seroconversion rates to influenza vaccine as healthy controls, but patients on ciclosporin and prednisolone exhibited reduced immunity.[380] Prednisolone at doses >10 mg/day did not affect the immune response to influenza vaccine, either in patients with chronic pulmonary disease in a prospective controlled trial[381] or rheumatoid arthritis.[211]

Pneumococcal vaccine: In two controlled studies, patients with rheumatoid arthritis on various anti-TNF agents achieved comparable protective anti-pneumococcal antibody titres compared to controls. Patients treated with MTX had reduced antibody titres to pneumococcal vaccination.[298,299] Prednisolone was not associated with reduced immunity. Renal transplant recipients on prednisolone (mean 18 mg/day) and azathioprine (mean 140 mg/day) had near normal immunity to pneumococcus following pneumococcal polysaccharide vaccine, compared to healthy controls.[382] Prednisolone at a dose >10 mg/day did not affect immunity to pneumococcus in patients with chronic pulmonary disease.[383]

Typhoid vaccine: In contrast, diminished cellular and humoral responses to the oral administration of *Salmonella enterica* 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.[384] 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.[385]

ECCO Statement OI 8H
Colectomy may impair the acquisition of immunity following oral administration of *S. enteritidis* serovar Typhi Ty21a vaccine, but not oral inactivated Cholera vaccine [EL2b, RG C]. Immunisation with parenteral *S. typhi* Vi polysaccharide is preferred in patients with inflammatory bowel disease who have had a colectomy [EL5, RG D]

Hepatitis A vaccine: In one study on the effect of HAV immunisation, 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 ($p<0.02$).[386] 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%. Immunity correlated with higher leukocyte and lymphocyte counts. No correlation was found with azathioprine or blood levels of calcineurin inhibitors.[387] Another study has reported seroconversion rates up to 41% in liver transplant patients and 24% in renal transplant patients after HAV immunisation.[388]

ECCO Statement OI 8I
All patients with inflammatory bowel disease should have Hepatitis A vaccination according to guidelines for the general population before travel to endemic areas. Response to Hepatitis A immunisation in immunocompromised patients with inflammatory bowel disease is unknown [EL4, RG C]. Monitoring the acquisition of immunity by repeat serologic assays should be considered [EL5, RG D]

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8.2. Travellers' diarrhoea

8.2.1. Background

Traveller's diarrhoea, which may be severe and incapacitating, is the most common health problem reported during travel to developing countries.[389] The duration is usually 1 to 5 days, but 5–10% of travellers report diarrhoea that lasts for 2 weeks or longer, and 1–3% report diarrhoea that lasts four weeks or longer.[390] It is unknown if patients with IBD are at higher risk for acquiring traveller's diarrhoea. However, this common disease, particularly if prolonged, may lead the traveller or the clinician to a wrong diagnosis of an exacerbation of IBD and to unnecessary self-treatment with medication for IBD. Nevertheless, infection with enteropathogens may provoke a relapse of quiescent IBD. Furthermore, travellers being treated with immunomodulators are at greater risk for acquiring food- and water-borne *Salmonella* sp., *Cryptosporidium parvum*, *Isospora belli*, *Microsporidia*, or *Cyclospora* sp. infection. For these reasons, patients with IBD should pay greater attention to precautions regarding food and water. *Cryptosporidium* is resistant to chlorination or iodination and prevention requires use of either boiled or filtered water, or commercially bottled beverages. Travellers are also best advised to avoid swallowing water while swimming in water that may be contaminated.

8.2.2. Treatment and self-treatment

Travellers to developing countries are often advised to carry a fluoroquinolone for empirical self-treatment of traveller's diarrhoea. Azithromycin, which was found to be comparable to quinolones[391] should be considered for self-treatment of traveller's diarrhoea in the following situations:

(i) patients who take a fluoroquinolone as part of their treatment for IBD
(ii) Travellers to countries where endemic bacteria are known to have high levels of fluoroquinolone resistance (e.g. Thailand and India)
(iii) Patients who have no response to a quinolone within 36–48 h
(iv) Pregnant women and children <16 years (for whom a fluoroquinolone is contraindicated).

Rifaximin (Xifaxan™, Salix Pharmaceuticals), an oral, non-absorbed rifamycin antibiotic, was approved for the treatment of traveller's diarrhoea caused by non-invasive strains of *E. coli* in patients aged >12 years. Rifaximin should not be used in patients with bloody diarrhoea or fever, or in patients who are suspected of having traveller's diarrhoea due to pathogens other than *E. coli* since rifaximin lacks efficacy against invasive pathogens (e.g. *Shigella*, *Salmonella*, and *Campylobacter* sp.). Since traveller's diarrhoea among patients with IBD has not been studied and IBD travellers may not themselves be able to determine the aetiology of their diarrhoea, empirical self-therapy with rifaximin cannot be advocated at this stage.

The immunocompromised traveller should have a lower threshold than immune competent travellers for initiating self-therapy for traveller's diarrhoea. If diarrhoea persists despite antimicrobial treatment efforts should be made to have a stool examination for ova and parasites.

ECCO Statement OI 8J
Patients with inflammatory bowel disease should pay greater attention to precautions regarding food and water during travel than normal. The immunocompromised patient should have a low threshold for initiating self-therapy for traveler's diarrhoea with quinolones or azithromycin, but not rifaximin. If diarrhoea does not improve within 48 h despite treatment, medical advice should be sought [EL5, RG D]

8.3. Screening for latent tuberculosis

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 travellers to high-endemicity countries, even if not engaged in health-care work, was substantial. It was of similar magnitude to the risk for the local population.[392] Though the risks and factors associated with acquisition of tuberculosis have not been defined in travellers with IBD, the clinician caring for patients with IBD may have to consider the following:

(i) Immunosuppression favours 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 travellers to these countries, who are at risk for tuberculosis, are best advised to have a tuberculin skin test or interferon-gamma release assay (QuantiFERON TB-Gold test, or ELISPOT) before departure.[287,393] If the result is negative, they should have a repeat test approximately 8–10 weeks after returning.[394,395] A two-step tuberculin skin test 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) Travellers with IBD to areas where tuberculosis is moderately to highly endemic and who are receiving immunomodulator therapy, regardless of the duration of travel
(ii) Travellers with IBD but without immunomodulators, who travel to areas where tuberculosis is moderately to highly endemic for a duration of 1 month or longer

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(iii) Travellers 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 young people with IBD who travel abroad before or after University, since they frequently travel for extended periods, stay in cheap accommodation, or engage in welfare projects that might put them at higher risk than older people who may travel in greater comfort. Of note, none of the current methods for pre- and post-travel TB screening approaches 100% sensitivity for diagnosing active tuberculosis.

ECCO Statement OI 8K
The risk of *M. tuberculosis* infection in long-term travelers to countries with high-endemicity is of similar magnitude to the average risk of the local population [EL2, RG B]. Patients with inflammatory bowel disease traveling for more than a month to a moderately or highly endemic area should be advised to have a tuberculin skin test or interferon-gamma release assay (IGRA) before departure. If negative, it should be repeated approximately 8–10 weeks after returning. Caution should be exercised in recommending IGRAs, since the predictive value in the immunocompromised is uncertain. Patients with inflammatory bowel disease on immunomodulators should avoid contact with TB patients [EL5, RG D]

8.4. Malaria

Unless pregnant, asplenic, or concomitant HIV infection, patients with IBD appear not to be at higher risk for acquiring malaria or the more severe complications of malaria compared to travellers without IBD, even when taking immunomodulators. Recommendations for malaria prevention, including prevention of mosquito bites and chemoprophylaxis, should be followed according to the existing guidelines. Interactions between antimalarial drugs and drugs for the treatment of IBD, particularly those that are new, should be taken into consideration. Metoclopramide decreases absorption of atovaquone (one of the demi-drug components of the anti-malarial drug Malarone) and may decrease the prophylactic efficacy.

8.5. Prevention of insect bites

Immunocompromised IBD travellers should take extra precautions to prevent bites of insects that are known to transmit diseases that are particularly severe in immunocompromised patients. Examples include reduviid bugs in rural Brazil and sandflies on beaches in exotic locations, which are the vectors of Chagas' disease and visceral leishmaniasis respectively. Patients taking immunomodulators should also be aware that infestation with scabies may lead to a severe variant (Norwegian, or crusted scabies) that is often complicated by secondary bacterial infection.

8.6. Guidelines for evaluating the returning traveller

It is beyond the scope of these guidelines to review the large number of diseases that may affect the returning traveller. 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 traveller).

8.6.1. General investigations

The returning traveller from long-term travel in developing countries is best advised to 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%.[396,397] 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.[397,398]

Parasitic infections are more likely to be diagnosed in patients with prolonged diarrhoea.[399] Common non-infectious causes of chronic diarrhoea in returning travellers include post-infectious 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.[397,400]

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.[401] Strongyloidiasis can persist indefinitely in a single host and cause hyperinfection years after acquisition when host immunity is impaired, especially by corticosteroid therapy. IBD patients returning from endemic areas (Section 5.4.1) are best evaluated for possible strongyloidiasis, even in the absence of symptoms or eosinophilia. The sensitivity of a single stool examination is low and repeated stool examinations are often needed. The diagnosis is often made by serologic tests[402] (Table 5). Many experts recommend therapy for seropositive patients, even if stool examinations are negative (Sections 5.4.2 and 5.4.3).

ECCO Statement OI 8L
Long term travellers with inflammatory bowel disease returning from developing countries should have a stool examination for bacterial pathogens, ova and parasites and a complete blood count to identify eosinophilia. For long term travellers with inflammatory bowel disease returning from countries highly endemic for strongyloidiasis, serological blood test for strongyloidiasis should be considered [EL5, RG D]

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9. Vaccination and systematic work-up to consider before introducing immunomodulator therapy

9.1. 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.

9.2. 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.

9.3. Laboratory tests

Many 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.

Ideally, baseline tests, potentially performed at diagnosis (see below), should include:

- Neutrophil and lymphocyte cell count
- C-reactive protein (a strikingly elevated CRP indicates an underlying infective process, but may also be caused by inflammation)
- 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 virus serology
- Human immunodeficiency virus (HIV) serology after appropriate counselling
- Eosinophil cell count, stool examination and strongyloidiasis serology (for returning travellers).

9.4. Screening for tuberculosis

Screening for tuberculosis should be considered 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 or interferon gamma release assay (according to country-specific guidelines).

9.5. 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, ideally at diagnosis for the reasons above:

- 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 polysaccharide vaccine
- Hepatitis B vaccine in all HBV seronegative patients.

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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