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ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease

T. Kucharzik[a]* , P. Ellul[b], T. Greuter[c], J.F. Rahier[d], B. Verstockt[e], C. Abreu[f], A. Albuquerque[g], M. Alloca[h], M. Esteve[i], F.A. Farraye[j], H. Gordon[k], K. Karmiris[l], U. Kopylov[m], J. Kirchgesner[n], E. MacMahon[o], F. Magro[p], C. Maaser, L[q]. de Ridder[r], C. Taxonera[s], M. Toruner[t], L. Tremblay[u], M. Scharl[v], N. Viget[w], Y. Zabana[i], S. Vavricka[v],
on behalf of the European Crohn's and Colitis Organisation [ECCO]

a. Department of Gastroenterology, Klinikum Lüneburg, University of Hamburg, Bögelstr. 1, 21339 Lüneburg, Germany
b. Department of Medicine, Division of Gastroenterology, Mater Dei Hospital, Msida, Malta
c. University Hospital Zürich, Department of Gastroenterology and Hepatology, Zürich, Switzerland; and Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois CHUV, University Hospital Lausanne, Lausanne, Switzerland
d. Department of Gastroenterology and Hepatology, CHU UCL Namur, Yvoir, Belgium
e. Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium and Department of Chronic Diseases, Metabolism and Ageing, TARGID - IBD, KU Leuven, Leuven, Belgium
f. Infectious Diseases Service, Centro Hospitalar Universitário São João, Porto, Portugal; Instituto de Inovação e Investigação em Saúde [I3s], Faculty of Medicine, Department of Medicine, University of Porto, Portugal
g. Gastroenterology Department, St. James University Hospital, Leeds, UK
h. Humanitas Clinical and Research Center – IRCCS -, via Manzoni 56, 20089 Rozzano [Mi] – Italy; Humanitas University, Department of Biomedical Sciences, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele – Milan, Italy
i. Hospital Universitari Mútua Terrassa, Digestive Diseases Department, Terrassa, Catalonia; Centro de Investigación biomédica en red de enfermedades hepáticas y digestivas CIBERehd, Madrid, Spain
j. Inflammatory Bowel Disease Center, Department of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL, USA
k. Department of Gastroenterology, Barts Health NHS Trust, Royal London Hospital, London, United Kingdom
l. Department of Gastroenterology, Venizeleio General Hospital, Heraklion, Greece
m. Department of Gastroenterology, Sheba Medical Center, Ramat Gan, Israel; Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
n. Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpital Saint-Antoine, Department of gastroenterology, Paris, France
o. Department of Infectious Diseases, Guy's and St Thomas' NHS Foundation Trust, London, UK
p. Gastroenterology Department, Centro Hospitalar São João, Porto, Portugal, Institute of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Portugal
q. Outpatient Department of Gastroenterology, Department of Geriatrics, Klinikum Lüneburg, University of Hamburg, Bögelstr. 1, 21339 Lüneburg, Germany

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r. Department of Paediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands
s. IBD Unit, Department of Gastroenterology, Hospital Clínico San Carlos and Instituto de Investigación del Hospital Clínico San Carlos [IdISSC], Madrid, Spain
t. Ankara University School of Medicine, Department of Gastroenterology, Ankara, Turkey
u. Centre Hospitalier de l'Université de Montréal [CHUM] Pharmacy Department and Faculty of Pharmacy, Université de Montréal, Montréal, Canada
v. University Hospital Zürich, Department of Gastroenterology and Hepatology, Zürich, Switzerland
w. Department of Infectious Diseases, Tourcoing Hospital, Tourcoing, France

Correspondence Torsten Kucharzik, Department of Gastroenterology, Klinikum Lüneburg, University of Hamburg, Bögelstr. 1, 21339 Lüneburg; e-mail: Torsten.Kucharzik@klinikum-lueneburg.de

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1. Introduction

The introduction and broad use of new immunosuppressive agents, including biologic agents and JAK inhibitors, have revolutionized treatment of inflammatory bowel disease [IBD] in recent decades. With such immunosuppression, the potential for opportunistic infection is a key safety concern. Opportunistic infections pose particular problems for the clinician; they are potentially serious, often difficult to recognize, associated with appreciable morbidity or mortality, and are challenging to treat effectively. The first guideline on opportunistic infections was published in 2009 [1] followed by an update in 2014.[2] New evidence in this field and in vaccination strategies for immunosuppressed IBD patients led the European Crohn's and Colitis Organization [ECCO] to update the previous consensus on opportunistic infections in IBD. The current document is focused on viral, mycobacterial, bacterial, fungal, and parasitic infections and on vaccination strategies for immunosuppressed IBD patients. The target audience includes IBD specialists, gastroenterologists, surgeons, and paediatricians.

To organize this work, 35 PICO questions were raised by the coordinators that address clinically relevant questions in opportunistic infections in IBD and in the field of vaccination. These were based on both the previous guidelines from 2009 and 2014 and on new relevant clinical questions in this field. The working group consisted of gastroenterologists, virologists, infectious disease experts, and paediatricians. Each PICO question was assigned to two working group members. As not all relevant clinical questions could be addressed by PICO questions, additional non-PICO questions that covered clinically relevant topics were drafted. In an initial teleconference in October 2019, all participants discussed the PICO and non-PICO questions and agreed on the final set of questions. The questions were classified into four major topics. The working groups then performed a systematic literature search of their topics with the appropriate key words using Medline/Pubmed, the Cochrane database, and their own files. The evidence level [EL] was graded according to the 2011 Oxford Centre for Evidence-Based Medicine [http://www.cebm.net/index]. Provisional guideline statements and recommendations, including supporting text, were then posted on a guideline platform with two subsequent online voting rounds where all participants could vote on the statements for the PICO and non-PICO questions. In the second round of voting, ECCO national representatives also participated in the voting process. The working group members then met over a final web-based video conference in September 2020 to discuss and vote on the statements and recommendations. Consensus was defined as agreement by 80% of participants, termed a consensus statement, and numbered for convenience in the document. Statements that are based on PICO questions are marked with a star [*].

The final document on each topic was written by the workgroup leader and their working party. Statements are intended to be read in context with supporting comments and not read in isolation. To ensure consistency, the statements and recommendations were rearranged and merged in the final manuscript by the coordinators. The final text was critically reviewed by external experts that were not involved in the guideline panel. The final manuscript was edited for consistency of style before being circulated and approved by the participants.

The final manuscript is divided into different sections that follow in a clinically relevant order but are not necessarily reflective of the order of the initial PICO questions. After a section on the definition of risk factors, the following sections focus on specific viral,

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mycobacterial, bacterial, and fungal infections. This is followed by special situations [such as travel to countries with endemic infections] and vaccination strategies in immunosuppressed IBD patients.
The level of evidence is generally low in some fields, which reflects the paucity of randomized controlled trials. Expert opinion has therefore been included where appropriate.

2. Definition and risk factors

2.1. Predictors of opportunistic infections in IBD

Statement 2.1
IBD patients at risk for opportunistic infections are those treated with immunosuppressive agents, particularly in combination [EL1]. Further predictive factors are malnutrition, obese BMI, comorbidities, active disease, and older age [EL3].

An opportunistic infection can be defined as a usually progressive infection by a microorganism that has limited or no pathogenic ability under ordinary circumstances but is able to cause serious disease as a result of the predisposing effect of another disorder or of its treatment.[2]
In general, risk factors for opportunistic infections in IBD patients are malnutrition, older age, congenital immunodeficiency, human immunodeficiency virus [HIV] infection, chronic diseases, diabetes mellitus, and use of immunosuppressive medication.[3-8] Risk factors can be categorized into 1] internal factors inherent to the patient [such as age, concomitant diseases, and malnutrition] and 2] external factors [immunosuppressive treatment, exposure to pathogens]. In IBD, immunosuppressive treatment increases the risk for opportunistic infections. Combination therapies in particular seem to increase this risk.[4] Several studies have assessed independent risk factors in more detail. The following additional risk factors were identified: overweight BMI, total parenteral nutrition, bowel surgery, presence of comorbidities, and IBD activity.[4, 9-14] While systemic steroids, thiopurines, and anti-TNF agents are all associated with an increased risk for opportunistic infections, combination therapies have a particular risk, with the odds ratio [OR] increasing from 2.9 [for one immunosuppressive drug] to 14.5 [for two or three]. The combinations of thiopurines plus steroids or thiopurines plus steroids plus infliximab appear to present the greatest risk.[4, 11] Specific immunosuppressive medications are associated with different infections; increased rates of fungal infections [*Candida*] have been observed with corticosteroid use, viral infections with thiopurines, and fungal and mycobacterial infections with anti-TNF agents.[4] Ongoing disease activity also increases the risk for infections. On the basis of 2266 Crohn's disease [CD] patients treated with adalimumab, each 100-point increase in the CD activity index [CDAI] is associated with a 30% increased risk of opportunistic infections.[12] Both malnutrition [OR 2.31] and obese BMI [OR 1.07 per kg/m^2] further increase the risk for such infections.[13, 14] No specific age cut-off can be given, as different thresholds are associated with increased risk for opportunistic infections,

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such as 45, 50, and 65 years. Older patients appear to be a particularly vulnerable population; there is an up to a 20-fold increased risk for patients >65 years who are treated with adalimumab or infliximab [rate of severe infections 11% vs 0.5%].[10]

2.2. What makes an IBD patient immunocompromised?

Statement 2.2

Immunosuppressive agents should be classified according to mechanism of action, dose, duration, and route of administration [EL5].

The term immunosuppressant as used throughout this manuscript includes systemic steroids, methotrexate, thiopurines, calcineurin inhibitors, vedolizumab, anti-TNF agents, IL-12/IL-23 antibodies, and JAK inhibitors. The different degrees of immunosuppression are specified in Table 1. The data on the impact of immunosuppressive drugs on the development of opportunistic infections are conflicting. A recent systematic review and network analysis [including 38 randomized controlled trials] did not detect a significant increase in infections with different treatments [including combination therapies] compared with placebo.[15] In addition, the SONIC trial revealed no differences between azathioprine alone, infliximab alone, and infliximab plus azathioprine combined.[16] In contrast, retrospective case-control studies and prospective registries showed an increased risk for patients on infliximab, steroids, azathioprine, or 6-MP and those on combination therapies.[4, 17] Infliximab confers a particularly high risk, which appears to be higher compared to other IBD therapies such as thiopurines.[17-19] A more recent meta-analysis of 15 observational studies showed an increased risk of infections with combination therapy compared to anti-TNF agents alone and with anti-TNF agents compared with other immunosuppressive agents.[20] Specific immunosuppressive drugs are associated with specific infection risks, such as mycobacterial and bacterial infection with anti-TNF agents and viral infection with thiopurines.[18, 21]

Vedolizumab shows a trend towards lower rates of non-gastrointestinal infections. No increases in opportunistic infections have been reported, likely due to its gut selectivity.[20, 22] However, enteric infections such as those caused by *Clostridioides difficile* may occur.[23]

No data are available comparing ustekinumab and tofacitinib with anti-TNF agents in IBD. However, recent data from rheumatology and dermatology suggest lower rates of serious infections with tofacitinib and ustekinumab compared to anti-TNF agents.[24, 25]

Table 1 categorizes IBD therapeutic agents into the following four degrees of immunosuppression: 1] no immunosuppression, 2] selective immunosuppression, 3] low immunosuppression, and 4] moderate-severe immunosuppression. Categorization of the degree of immunosuppression is required to assess the [potential] risk of opportunistic infections in an individual patient and to decide if live vaccines can be administered safely. There are still nuances of immunosuppression in particular within the group of “moderate-

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severe immunosuppression" that cannot be completely reflected by this category. Since data directly comparing different conventional immunosuppressive drugs and different biologics are limited, it is not possible to clearly and unambiguously differentiate between moderate and severe systemic immunosuppression. While calcineurin inhibitors [ciclosporin, tacrolimus], anti-TNF agents, tofacitinib, and ustekinumab are all considered to induce moderate-severe immunosuppression, for other agents the degree of immunosuppression depends on mechanism of action, dose, duration, and route of administration. The distinction between no, selective or low-degree immunosuppression, or moderate-severe immunosuppression has direct clinical implications. While live vaccines are contraindicated in patients with moderate-severe immunosuppression, administration of such vaccines can be discussed on a case-by-case basis for patients with selective or low-degree immunosuppression, if benefit from vaccination outweighs the risk [see section 8.2]. Methotrexate can be considered low-degree immunosuppression if administered at a dose ≤0.4 mg/kg/week [corresponding to ≤20 mg per week].[26] Similarly, azathioprine at doses of ≤3 mg/kg/day and 6-MP at doses of ≤1.5 mg/kg/day can be considered low-degree immunosuppression.[26] For steroids, dose, duration, and whether they act topically or systemically must be considered. Long-term maintenance treatment with topical oral budesonide up to 6 mg/day did not result in higher rates of infections compared with placebo.[27, 28] At the other end of the spectrum, treatment with systemic steroids at doses of ≥20 mg for >2 weeks is considered moderate-severe immunosuppression based on a relative risk [RR] for infections of 1.85 when compared to a RR of 1.10 for doses at <5 mg/day in patients >65 years.[29]

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Table 1: IBD therapeutic agents and different degrees of immunosuppression

Drugs	Degree of immunosuppression	Comment
Aminosalicylates		No systemic effects
Topical steroids		Systemic immunosuppression with oral topical steroids [oral budesonide] at doses >6 mg/day.
Systemic steroids		Moderate-severe immunosuppression with doses of ≥20 mg for >2 weeks.
Vedolizumab		Gut-selective treatment. No systemic effects, but increased risk for intestinal infections
Methotrexate		Moderate-severe immunosuppression with >20 mg per week [>0.4 mg/kg/week]. Lower doses can be considered as low immunosuppression.
Azathioprine/6-MP		Moderate-severe immunosuppression with >3 mg/kg/day [AZA] or >1.5 mg/kg/day [6-MP]. Lower doses can be considered as low immunosuppression.
Ciclosporin		There are different nuances within the group of moderate-severe immunosuppression that cannot be reflected by this simplified category. For instance combination therapy [combination of any of these or combination with other immunosuppressive drugs such as AZA, methotrexate, or steroids] results in an increased risk for opportunistic infections.
Tacrolimus		
Anti-TNF		
Tofacitinib		
Ustekinumab		

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		Immunosuppression of Anti-TNF is probably higher compared to ustekinumab and tofacitinib

Simplified degree of immunosuppression (The table helps to decide if live vaccines can be administered safely):

No:

Selective:

Low:

Moderate-severe:

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3. Viral infections

3.1. General aspects

Statement 3.1*
Serologic screening for hepatitis A, B, C, HIV, Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, and measles virus [in the absence of documented past infection or vaccination for the latter two] is recommended for all IBD patients at baseline [EL4] and especially prior to or during immunosuppressive treatment [EL1]. A Pap smear for human papillomavirus screening is also recommended [EL1].

Although several cohort studies worldwide indicate that the prevalence of hepatitis B virus [HBV], hepatitis C virus [HCV], and human acquired immunodeficiency virus [HIV] in IBD patients is similar to the general population, case-control data are scarce and influenced by geographical area of origin.[30]and[31]

The fatality rate of fulminant hepatitis A virus [HAV] infection has been estimated to be up to 2.1% in adults >40 years and a higher rate is suggested in immunosuppressed patients.[32] The risk of cytomegalovirus [CMV] reactivation is increased in IBD patients exposed to corticosteroids or thiopurines but not with anti-TNF agents.[33] Colectomy within 12 months of hospitalization for acute severe ulcerative colitis [UC] is associated with a higher CMV prevalence.[34] CMV-seropositive patients receiving immunosuppressants are at risk of end-organ reactivation, whereas seronegative patients acquire primary CMV infection infrequently. Epstein-Barr virus [EBV] was detected in 75% of IBD patients on anti-TNF agents and other immunosuppressants with an increased risk of lymphoma (OR: 4.20; 95% confidence interval [CI]: 1.35–13.11) in a case-control study.[35] Primary EBV infection in EBV-negative patients appears to be a risk factor for lymphoproliferative disease, although the absolute risk is low.[36]

Thus, measurement of IgG antibodies against HAV, HBV, HCV, HIV, EBV, and CMV is recommended for all IBD patients preferably at disease diagnosis, or at least before starting or while being treated with immunosuppressive agents, if baseline measurements are missing.

IBD patients on immunosuppressants have an increased risk of cervical high-grade dysplasia or cancer [OR: 1.34; 95% CI: 1.34–1.46] compared with the general population.[37] A pap smear for HPV screening is therefore recommended at disease diagnosis for all female patients with IBD.

Immunosuppressed individuals who are seronegative for varicella-zoster virus [VZV] IgG are at risk of severe varicella and require prompt post-exposure prophylaxis in the event of exposure. Determination of the serological status in patients without prior documented chickenpox, shingles, or vaccination identifies candidates for varicella vaccination. An increased risk of herpes zoster [HZ] infection has also been observed in IBD compared to

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non-IBD patients [RR 1.74; 95% CI: 1.57–1.92 for CD and RR: 1.40; 95% CI: 1.31–1.50 for UC].[38] A dose relationship was observed in moderate-to-severe UC patients treated with tofacitinib (overall incidence rate [IR]: 4.1; 95% CI: 3.1–5.2)[39] and IBD patients treated with JAK inhibitors [OR 1.57; 95% CI: 1.04–2.37].[40]

3.2. Hepatitis A-E

Statement 3.2
In non-immune patients, vaccination for HAV should be considered prior to commencement of immunosuppressive treatment [EL5].

3.2.1. Hepatitis A virus and vaccination

A HAV vaccine is usually administered to children from 12 months of age. Older children and adults can also be vaccinated. It should be administered to those in at-risk groups or for travel to countries where hepatitis A is common. Seroconversion is usually 94–100% after the second dose and can last for more than 25 years in adults.[41, 42] The absolute lower limit of anti-HAV Ab required to prevent HAV infection has not been defined. Antibody quantification is not recommended, as the sensitivity of current tests is variable.[41, 43, 44]

In a study by Park *et al.*, the seroconversion rate in IBD patients after HAV vaccination was 97.6%. However, this was significantly lower in patients treated with anti-TNF agents [92.4% vs 99.1%; $p = 0.001$]. In addition, the seroconversion rate was significantly lower in patients treated with more than two than with one immunosuppressant [92.6% vs 98.4%; $p = 0.03$].[42]

Current recommendations suggest post-exposure prophylaxis [vaccine and immunoglobulin 0.1 mL/kg] within 14 days of exposure for unvaccinated, immunosuppressed patients.[45]

3.2.2. Hepatitis B virus

3.2.2.1. Vaccination against HBV

Statement 3.3*
Patients with IBD should be vaccinated against hepatitis B to achieve an anti-HBs antibody level >10 IU/L [EL1].

Reactivation of HBV is a well-known complication of immunosuppression. In retrospective cohort studies assessing the outcome of HBV infection in IBD patients, liver failure due to

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viral reactivation has been described in a high percentage of immunosuppressed patients.[46, 47] Current guidance therefore suggests that all patients with IBD should be vaccinated against HBV. An anti-HBs IgG >10 IU/L is consistent with response to vaccination. Retrospective analysis revealed that previously vaccinated patients frequently did not have anti-HBs IgG >10 IU/L.[48-50] Vaccine response should therefore be tested following a standard course of vaccination, and further doses of standard or higher-dose vaccine should be administered in accordance with national or regional guidelines to achieve anti-HBs IgG > 10 IU/L if possible. [48-50]

In a meta-analysis of 1688 IBD patients, the response rate to vaccination was 61% [95% CI: 53–69]. Young age [mean difference: 5.7; 95% CI: -8.48 to -2.95] and vaccination during remission [RR: 1.61; 95% CI: 1.15–2.29] were associated with a satisfactory response to vaccination. Not being on immunosuppressive therapy was predictive of an immune response compared to being on immunosuppressive therapy [RR: 1.35; 95% CI: 1.13–1.59], immunomodulatory therapy [RR: 1.33; 95% CI: 1.08–1.63], or anti-TNF agent [RR: 1.57 95% CI: 1.19–2.08].[50] In studies where patients with IBD were re-vaccinated, higher rates of seroconversion were obtained following revaccination and varied with the number and dosage of vaccinations.[51, 52]

3.2.2.2. Antiviral treatment for chronic hepatitis B

Statement 3.4*
Patients with IBD and chronic hepatitis B infection should be treated with specific antiviral nucleos[t]ide analogues [EL1].

Reactivation of hepatitis B infection in patients receiving immunosuppressive treatment is associated with mortality rates of approximately 5%.[53]

Studies on immunosuppressed IBD patients with chronic hepatitis B [CHB] [HBsAg-positive] revealed that patients on prophylaxis with anti-hepatitis B nucleos[t]ide analogues [NA] had a lower reactivation rate [7.1%] than patients not receiving prophylaxis [47.4%].[51, 54, 55]

Similarly, 39% of CHB patients using anti-TNF agents had reactivation; this was higher in patients previously treated with immunosuppressants [96% vs 70%; p = 0.033] and lower in those who received antiviral prophylaxis [23% vs 62%; p = 0.003].[56]

Furthermore, Esteve *et al*. noted HBV reactivation in 2 [n=3] CD patients on withdrawal of infliximab therapy. No reactivation occurred in the third patient who was on NA prophylaxis.[57]

For decades, long-term prednisone, azathioprine, or both have been known to favour the replication of HBV in patients who are HBsAg positive.[58]

It is recommended that CHB patients should ideally start prophylaxis [tenofovir or entecavir] 2 weeks prior to the introduction of immunosuppressants and this should be continued for

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at least 12 months after immunosuppressant withdrawal and discontinued only if the underlying disease is in remission. Liver-function tests and HBV DNA should be tested every 3 to 6 months during prophylaxis and for at least 12 months after discontinuation.[59] [53]

3.2.2.3. Antiviral treatment for occult hepatitis B

Statement 3.5*
Prophylactic treatment with antiviral agents is not recommended in patients with IBD and prior HBV infection [HB core Ab-positive, HBsAg-negative] [EL3].

Patients with evidence of prior HBV infection [HB core Ab-positive, HBsAg-negative] do not require antiviral prophylaxis. In an analysis of five studies on immunosuppressed IBD patients who were HB core Ab-positive, HBV reactivation occurred in 0.28% of patients.[51, 54, 55, 60, 61] In patients receiving anti-TNF agents for various conditions, including IBD, Perez-Alvarez *et al*. found a reactivation rate of 5%.[56]

In HBsAg-negative, anti-HBc-positive patients with moderate [<10%] or low [<1%] risk of HBV reactivation, a pre-emptive therapy approach is recommended. This entails monitoring HBsAg or HBV DNA [or both] every 1–3 months during and for at least 6 months after stopping immunosuppression. In the event of reactivation [detectable HBV DNA or HBsAg seroconversion], pre-emptive therapy with anti-hepatitis B nucleos[t]ide analogues should be commenced.[59] Consultation with a hepatologist or infectious disease specialist should be sought in unclear situations.

3.2.3. Hepatitis C

Statement 3.6*
Patients with IBD and hepatitis C should be treated in accordance with national and international guidelines [EL5].

Patients with IBD and hepatitis C should be closely monitored for disease exacerbation when being treated with direct-acting antiviral agents [DAAs] [EL5].

3.2.3.1. Antiviral treatment

Hepatitis C treatment has been revolutionized in recent years, moving from pegylated interferon-α [Peg-IFN α] with ribavirin to DAAs. DAAs are now the recommended standard-of-care treatment for HCV.

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There are no clinical trials on the safety and efficacy of DAAs for the treatment of HCV infection in patients with IBD. Information is largely restricted to a few case reports and case series. The sustained virological response [SVR] in IBD patients under immunosuppression is largely unknown. A case series of three patients requiring immunosuppression with adalimumab, carboplatin/irinotecan, or capecitabine, respectively, reported a SVR after completion of DAA therapy in all patients. SVR after DAA therapy did not seem to be affected by immunosuppressive therapy.[62] A case report of a patient with HCV genotype 2b treated with sofosbuvir and ribavirin and with clinically active disease during therapy revealed improvement after ribavirin reduction and achievement of SVR at 12 weeks. [63] SVR was also achieved in another case of a CD patient with short-bowel syndrome who was treated with sofosbuvir and ledispavir for 12 weeks.[64] The possibility of new-onset colitis after starting treatment with sofosbuvir and simeprevir [65] [66] has been reported in 2 patients with HCV genotype 1 without a previous IBD diagnosis.

3.2.4. Hepatitis E Virus

The clinical features of acute hepatitis E are similar to those of other acute viral hepatitis. In immunocompetent persons, acute illness is infrequent and often mild due to brief viraemia.[67] Ribavirin therapy for 3 weeks in patients with severe hepatitis E leads to rapid improvement of liver enzymes and function.[67, 68]

Current European Association for the Study of the Liver recommendations suggest a combination of serological assays and nucleic acid amplification technology [NAT] testing to diagnose acute and chronic hepatitis E. Anti-hepatitis E virus [HEV] antibodies are often undetectable in immunosuppressed patients and NAT is the only reliable method of diagnosis.[69]

HEV genotype 3 causes severe disease, including chronic hepatitis E, in immunosuppressed persons. Chronic infections do not occur in otherwise healthy individuals.[67, 68, 70]

Individuals receiving immunosuppressive treatment may fail to clear the virus from blood and stool and are at risk of progression to chronic hepatitis E [disease lasting >6 months]. The clinical manifestation and progression of chronic hepatitis E are variable; some cases progress to significant fibrosis in a relatively short period of time. Reducing immunosuppression leads to viral clearance in a significant proportion of patients. Ribavirin is the drug of choice for patients with persistent viraemia that lasts for 3 months.[67, 70] There is currently no licenced vaccine for HEV.[68] A study by Senosiaina *et al.* revealed that the seroprevalence of HEV in IBD patients is up to 1.14%, similar to that in the general population, with negative HEV RNA even in those on immunosuppressants.[71]

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3.3. HIV infection

Statement 3.7*
IBD patients with HIV infection can be treated with immunosuppressive therapy when on antiretroviral therapy with stable CD4 counts and undetectable viral load. The CD4 count should be closely monitored [EL4].

Although HIV-infected patients seem to receive fewer immunosuppressive treatments compared to non-HIV-infected IBD patients, the course of IBD did not differ between these groups in a recent large cohort study, suggesting that HIV infection might attenuate IBD [72]. HIV-infected patients with stable CD4 counts requiring immunosuppressants do not appear to be at increased risk of opportunistic infection. In a case series of 7 HIV-infected patients on antiretroviral therapy [ART] treated with azathioprine for various inflammatory conditions [including IBD], there were no serious opportunistic infections either during or in the 6 months after stopping azathioprine. Although 2 patents died, this was not attributable to azathioprine.[73] TNF-α activates viral replication and pathogenesis of HIV-1.[74] In a systematic review on the efficacy and safety of six biologics [rituximab, etanercept, adalimumab, alefacept, infliximab, ustekinumab] for several inflammatory conditions [including 3 IBD patients] in HIV-infected individuals,[75] there were 37 treatment episodes described and 33 episodes [89%] where anti-TNF agents were used. While the efficacy and the infectious and non-infectious complications were comparable to reports from HIV-uninfected patients, the evidence was of low quality and the data were heterogeneous. In another systematic review of 27 cases of HIV-positive patients on anti-TNF agents [infliximab, adalimumab, or etanercept only] for several inflammatory conditions [2 with CD], there were four patients with infectious complications, with one death due to sepsis [infected catheter] while the patient was on etanercept [CD4 count 20 cells/mm^3, viral load 14 000 copies/mL].[74]

Vedolizumab has shown some benefits in sustained virological control of the simian immunodeficiency virus.[76] In a case report, an HIV-infected man with CD achieved clinical remission with vedolizumab while on ART therapy [1-year follow up].[77] While vedolizumab might in theory be a more appealing drug in the HIV setting [gut selectivity, low rate of serious infections, and potentially good effect on HIV][77], more data are needed.

In a case series of 13 patients with HIV-associated psoriasis, the 4 patients that received methotrexate developed leukopenia with 1 patient developing toxic encephalopathy. One of these methotrexate-treated patients with leukopenia was diagnosed with *Pneumocystis jiroveci* pneumonia and *Staphylococcus* sepsis after the drug was discontinued.[78],[79]

Possible side effects should be monitored in patients treated with steroids, especially those treated with ritonavir, which can potentiate their effects. Other interactions between HIV drugs and immunosuppressive therapy can also occur.[75]

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3.4. Herpesviruses [HSV, VZV, CMV, EBV]

3.4.1. Herpes simplex virus

Primary or recurrent oral and genital herpes may be more frequent, severe, and extensive in immunocompromised patients.[80, 81] Herpes simplex virus [HSV] can cause severe disease in immunocompetent individuals, including keratitis, encephalitis, and retinitis.[80] In a prospective study, IBD patients receiving azathioprine therapy self-reported significantly more skin or genital herpes flares than patients on mesalazine.[82] Reactivation may cause severe localized systemic infections with significant morbidity and mortality, including encephalitis,[83, 84] meningitis,[85] pneumonia,[86] oesophagitis,[87] and colitis.[88, 89] There is no vaccine available for HSV. Patients should be asked if they have a history of HSV infection prior to commencing immunosuppressive therapy. Routine prophylaxis to suppress virus replication should be considered for patients with frequent recurrent attacks, who are already taking intermittent suppressive antiviral therapy, or both. Acyclovir 400 mg twice daily, valacyclovir 500 mg daily, or famcyclovir 250 mg twice daily are suitable as prophylaxis. [90]

3.4.2. Varicella zoster virus

Statement 3.8*

Recombinant herpes zoster vaccine [RZV] is the preferred vaccine for patients with IBD disease given its efficacy and safety [EL3]. If RZV is not available, a live zoster vaccine [ZVL] is recommended in immunocompetent patients with IBD aged ≥50 years [EL4].

RZV remains recommended for patients with IBD receiving immunosuppressive therapy [EL4]. If RZV is unavailable, ZVL may be considered in patients on low-dose immunosuppression [EL3].

IBD confers a significant risk of developing symptomatic varicella zoster reactivation; this risk increases with age. The relative risk of HZ in patients with CD and UC is 1.74 [95% CI: 1.57–1.92; $p < 0.001$] and 1.40 [95% CI: 1.31–1.50; $p < 0.001$], respectively.[91] The risk to patients receiving immunosuppressive therapy is further increased. In CD, a retrospective cohort study revealed that corticosteroid use conferred a RR of 1.78 [95% CI: 1.10–2.88]; in UC, steroids and anti-TNF agents conferred a RR of 1.99 [95% CI: 1.64–2.42] and 2.29 [95% CI: 1.52–3.45], respectively.[92]

Prior to development of the RZV, only the ZVL was available. In a large retrospective cohort study, vaccination with ZVL was associated with a significantly lower infection rate in IBD patients [OR: 0.54; 95% CI: 0.44–0.68].[93] This cohort included a population of 59 individuals on anti-TNF agents who received ZVL, including 12 [20%] who were also taking thiopurines.[94] No cases of disseminated varicella infection were observed within 42 days of vaccination.

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The evidence to support the efficacy of ZVL in immunosuppressed patients is conflicting. A sub-analysis of the cohort above who were prescribed thiopurines and received vaccination [n=315] failed to demonstrate reduced HZ compared with those receiving thiopurines who were not vaccinated [n=3892] [adjusted HR: 0.63; 95% CI: 0.30–1.33].[93] Wasan *et al*. observed a blunted immune response in patients with IBD on immunosuppressive therapy.[95] A post-hoc sub-analysis of a large RCT of rheumatoid arthritis [RA] patients treated with tofacitinib, tofacitinib and methotrexate, or adalimumab also failed to demonstrate a significant reduction in HZ in the vaccinated group [3/209 vs 9/397; p = 0.70].[96] However, a second large database study did suggest efficacy in those inadvertently vaccinated whilst receiving anti-TNF agents; of 551/66751 patients with IBD on anti-TNF agents, none developed HZ within 42 days and ZVL was associated with fewer cases in the 2-year follow up [OR: 0.61; 95% CI: 0.52–0.71].[97]

The commercial availability of RZV provides an alternative to ZVL. A phase 3 RCT revealed a vaccine efficacy of 97.2% [95% CI: 93.7–99.0; $p < 0.001$] in participants aged ≥50 years.[98] The safety and immunogenicity of RZV has been demonstrated in patients with immune-mediated disorders [n=1943], including a small number of patients with CD [n=28] and UC [n=61].[99] A phase 3 placebo-controlled RCT evaluated the efficacy of RZV in recipients of haemopoietic stem-cell transplants.[100] This study demonstrated an estimated vaccine efficacy of 63.8% [95% CI: 48.4–74.6], but also revealed more injection-site reactions in the treatment arm [risk difference: 22.6%; 95% CI: 18.5–26.6; $p < 0.0001$]. A single retrospective cohort study evaluating immunosuppressed IBD patients receiving RZV was presented recently, with data supporting the accumulating published evidence that RZV is effective in immunosuppressed patients [OR: 0.36; 95% CI: 0.23–0.56].[101]

Studies of vaccination against VZV in the IBD population have involved patients aged ≥50 years. However, it is known that patients of all ages treated with tofacitinib are at higher risk of shingles [OR: 3.65; 95% CI: 2.74–4.76 for patients <65 years; OR: 9.55; 95% CI: 4.77–17.08; for patients ≥65 years].[102] In addition, the European Medicines Agency Committee for Medicinal Products for Human Use released a statement supporting extension of use of RZV to those aged ≥18 years who are at additional risk of HZ,[103] although evidence to support use of RZV in younger adults is scarce.

Patients naïve to varicella zoster virus

Adult patients with IBD ideally should have received the varicella vaccine during childhood. Universal vaccination has been recommended since 1995 in the United States.[104] However, only certain countries in the European Union have varicella vaccine programs. Patients with IBD with a history of varicella [chickenpox] or documented vaccination should be considered as protected. Commercially available serological testing for VZV may be insensitive for detecting low-level antibodies and may yield false-negative results. Such testing should be used only in patients without documented infection or completion of the vaccination series.[105] In recent years, more sensitive, quantitative commercial assays have become available. Varicella vaccination consists of two doses given 4–8 weeks apart. The varicella vaccine is a live vaccine with the same viral strain as ZVL but 14 times less concentrated.

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Varicella and ZVL vaccines are contraindicated in patients with a moderate-to-severe degree of immunosuppression and should be completed 4 weeks before starting immunosuppressive therapy [see section 8.2]. The Infectious Diseases Society of America clinical practice guideline states that administration of varicella vaccine can be considered for non-varicella immune patients who are receiving low-dose immunosuppression.[106]

3.4.3. Cytomegalovirus infection

Statement 3.9*

Concurrent CMV colitis worsens the prognosis of active IBD. Patients with refractory IBD should be tested for CMV colitis [EL3], especially if they are not responding to immunosuppressive therapy [EL2].

3.4.3.1. When to test?

The prevalence of CMV colitis in different studies is variable depending on the diagnostic tests used and the population studied. The prevalence ranges from 10–30% in steroid-refractory acute colitis.[107] Concurrent CMV colitis is associated with a major risk of poorer outcomes, including toxic megacolon, colectomy, rescue therapy, and increased rate of disease flares. [108-113] A recent retrospective cohort study of 257 UC patients followed for 10 years revealed that CMV colitis was an independent predictor of hospitalization and surgery [HR: 2.27; 95% CI: 1.12–4.60].[114] Finally, a meta-analysis revealed that IBD patients with concurrent CMV infection had a poorer prognosis than patients without CMV.[115] Therefore, there is evidence to support screening for CMV colitis in patients with active severe IBD.

Refractory disease [OR: 4.24; 95% CI: 2.21–8.11], immunosuppressive agents such as azathioprine or methotrexate [OR: 1.95; 95% CI: 1.05–3.62], and age >30 years were significantly associated with CMV disease in a retrospective case-control study of 68 patients with IBD.[116] The use of anti-TNF agents was an independent risk factor for CMV colitis [OR: 11.13; 95% CI: 3.31–37.44] in another retrospective cohort study.[117] Other studies found an association with immunosuppressive therapy and steroid refractoriness.[118, 119] A multicentre retrospective study in 56 children with acute severe UC found a higher prevalence of CMV disease in steroid-refractory patients.[34] Four meta-analyses assessed the relationship between CMV infection and use of immunosuppressants.[120-123] Concurrent CMV infection increased the risk of steroid refractoriness by 2.34 fold in IBD patients compared with patients without CMV.[120] Exposure to thiopurines [OR: 1.56; 95% CI: 1.01–2.39] but not to anti-TNF agents increased the risk of CMV reactivation.[123] These data support the recommendation to screen for CMV colitis in active IBD patients who are not responding to immunosuppressive therapy.

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Statement 3.10*
Immunohistochemistry [IHC], possibly tissue PCR, or both are essential for confirming active CMV infection [colitis] in IBD and should be the standard tests [EL2]. Findings and potential interventions should be discussed in the clinical context.

3.4.3.2. Testing for CMV infection

A meta-analysis by Tandon *et al*. assessed the accuracy of blood-based versus tissue-based tests for detecting CMV. The overall pooled sensitivity of blood-based tests was 50.8% [95% CI: 19.9–81.6], 39.7% [95% CI: 27.4–52.1] for pp65 antigenemia assay, and 60.0% [95% CI: 46.5–73.5] for blood PCR [bPCR].[124]

The overall pooled specificity of blood-based tests was 99.9% [95% CI: 99–100], 90.7% [95% CI: 86.1–95.4] for pp65 antigenemia assay, and 100% for bPCR with a positive predictive value [PPV] of 83.8% [95% CI: 58.6–95.0] and a negative predictive value [NPV] of 80.3% [95% CI: 69.8–87.7].

There is no cut-off level for blood CMV DNA to distinguish latent from active infection. Cut-offs in post-transplant patients vary from 4000 to 10 000 IU/mL.[125, 126] In a recent study on diagnosing suspected CMV colitis in patients with moderate-to-severe UC, serum DNA PCR positivity was defined as >250 copies/mL. The sensitivities of the CMV antigenemia and serum CMV DNA PCR tests were relatively low [47.0% and 44.3%, respectively]; however, the specificities were high [81.7% and 87.9%, respectively].[127]

Colonic tissue tests were also analysed in a meta-analysis. The overall pooled sensitivity of haematoxylin and eosin staining [H&E] for CMV reactivation was 12.5% [95% CI: 3.6–21.4], 34.6% when compared with IHC as the reference test [95% CI: 13.8–55.4], and 4.7% when compared with tissue PCR [tPCR] as the reference test [95% CI: 1.2–17.1].[128]

The PPV and NPV of H&E for predicting colonic CMV reactivation was 77.4% [95% CI: 47.9–92.8] and 56.4% [95% CI: 23.3–84.6], respectively.

An analysis to assess the sensitivity of IHC compared with tPCR as the reference standard revealed that IHC had a sensitivity and specificity of 23.0% [95% CI: 8.8–48.0] and 98.7% [95% CI: 93.9–99.7], respectively.

Although a definite cut-off has not yet been agreed on, Roblin *et al.*[129] suggested a viral load cut-off of >250 viral copies/mg tissue. When assessing for CMV colitis, biopsy location and number appear to be important. Mucosa that is not actively inflamed does not usually reveal CMV DNA.[129] Tissue from the base and edges of ulcers were found to have the highest densities of CMV-positive cells.[130]

Left-colon biopsies identify most UC patients with CMV. Conversely, in CD many patients had CMV detectable only in right-colon biopsies. A minimum of 11 biopsies for UC and 16

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biopsies for CD was proposed by McCurdy *et al.*[131] to achieve an 80% probability of CMV detection.

A recent retrospective study on 25 IBD patients with positive tPCR found that while 60% of patients with IHC or tPCR positivity and 80% with H&E, IHC, or tPCR positivity underwent surgery, only 26.8% of the patients with exclusively PCR positivity underwent surgery.[132]

The clinical significance of a positive PCR of colonic tissue without other histological signs of infection remains unclear. Tissue CMV PCR analysis for diagnosis of CMV colitis is not well standardized and cut-off values for different tests are not available.

Finally, given the reduced sensitivity of blood-based testing and histology [H&E stain], IHC, possibly tPCR, or both are essential for detecting CMV colitis in IBD and should be considered as standard tests.[124] There is no evidence to suggest any cut-off levels.

Blood-based tests may be considered in addition to tissue-based tests when considering cessation of immunosuppressive therapy.

It remains unclear how the resolution of the CMV colitis should be determined.[133]

Statement 3.11*

Immunosuppressive therapy should not be discontinued in IBD patients with intestinal CMV reactivation in general [EL3]. Steroids should be tapered [EL4].

Antiviral therapy should be considered in steroid-refractory IBD patients with CMV colitis [EL3].

Discontinuation of immunosuppressive therapy is recommended in symptomatic disseminated CMV infection [EL 4].

3.4.3.3. How to deal with immunosuppressive treatment?

CMV is frequently detected in colonic tissue of IBD patients who are refractory to immunosuppressants; CMV is considered to be involved in the pathophysiology of steroid refractoriness. [111, 117, 131] This form of CMV infection is a localized tissue-invasive disease involving the gastrointestinal tract, mainly colonic tissue in UC.

There have been no studies specifically designed to address immunosuppressive treatment in this clinical scenario.

Corticosteroids [OR: 2.05; 95% CI: 1.40–2.99] and azathioprine [OR: 1.56; 95% CI: 1.01–2.39] are independent predictive factors of CMV reactivation in the colon, which in turn may aggravate moderate or severe attacks of IBD.[123]

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Based on this indirect information or mechanistic hypothesis, several therapeutic schedules have been proposed, such as rapid steroid tapering [108] [134] or administration of infliximab, which is considered to have a lower risk of CMV reactivation than other immunosuppressants, such as thiopurines.[116, 123] Recently, two case reports proposed vedolizumab for the treatment of steroid-resistant colitis with CMV reactivation,[135] [136] although its efficacy has not been shown in large cohorts.

Although immunosuppressants could theoretically worsen the outcome of CMV colitis, many case series and retrospective cohorts have shown that immunosuppressants are maintained for control of disease activity in most cases.[108, 111, 117, 131, 134, 137, 138] [139-143] [144] [145] Moreover, CMV clearance may parallel the achievement of remission induced by immunosuppressants, even in patients that did not receive antivirals. This occurs more frequently in patients with low viral load and a low number of IHC-positive cells in the colon.[139] A case-control study with a very limited number of UC cases reported that immunosuppressant discontinuation plus antivirals achieved remission and colectomy rates similar to refractory patients without CMV managed with standard rescue therapy.[146] Thus, the best therapeutic schedule for CMV reactivation in refractory UC remains to be determined.

Case reports have described severe disseminated CMV infection, generally primary CMV infection.[147] These cases are characterized by a mononucleosis-like syndrome or CMV syndrome [positive serum PCR with fever, malaise, leukopenia, low platelet count, and elevated liver enzymes].[148]. In these severe cases, discontinuation of immunosuppressive therapy is recommended.

Two meta-analyses revealed contradictory results regarding the benefits of antiviral therapy in CMV reactivation in IBD, probably due to differences in CMV burden.[149, 150] There is limited information on the relationship between the evolution of UC and tissue viral load, as measured by viral inclusions in IHC [151, 152] or CMV DNA copies.[129] In this sense, some studies demonstrated that the higher the colonic viral load, the higher the risk of colectomy, supporting the benefit of antiviral therapy in CMV reactivation in UC in most patients. However, an exact threshold to determine which patients might benefit from antiviral therapy is currently unknown. This aspect should be considered in further prospective studies.

Intravenous ganciclovir 5 mg/kg twice daily for 5–10 days followed by valganciclovir 900 mg daily until completion of a 2–3 week course is the treatment of choice. An earlier transition to oral treatment is possible depending on the treatment response. [148] The common side effects of ganciclovir, namely neutropenia and thrombocytopenia [also manifestations of systemic CMV], can add complexity to management. Such situations require a multidisciplinary approach, including engagement with infectious disease specialists. Foscarnet may be used for ganciclovir-intolerant patients, or in uncommon cases of ganciclovir-resistant CMV. Strict monitoring of renal function and bivalent electrolytes is required. Concomitant administration of normal saline may reduce the risk of irreversible renal damage. High levels of this drug are excreted in the urine and may be associated with significant irritation and ulceration in the genital area. Careful hygiene can mitigate this risk.

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3.4.4. Treating IBD patients with EBV and on immunosuppressive treatment

Statement 3.12*
EBV is associated with an increased risk of lymphoma in EBV-negative patients on immunosuppressive therapy, primarily thiopurines [EL4]. Use of thiopurines in EBV-IgG negative patients should be carefully considered [EL5].

Following primary infection in a normal host, T cells mediate lifelong control of proliferation of EBV-infected B cells. Prospective assessment of EBV serology in paediatric and adult IBD cohorts demonstrated that in most patients, EBV infection is a self-limiting illness or is asymptomatic, even in patients receiving immunosuppression.[153, 154] Impairment of T-cell function may lead to loss of control over B-cell proliferation with a potential risk of B-cell lymphoma.[155, 156] [157] [158-160] The vast majority [up to 95%] of the adult population is EBV seropositive due to childhood or adolescent exposure.[161, 162] In EBV-IgG negative post-transplant patients treated with immunosuppressive therapy, primary EBV infection increases the risk of post-transplant lymphoproliferative disease.[163, 164] In IBD, such an association is less well established. Treatment with thiopurines alone or in combination with anti-TNF agents is associated with an increased risk of lymphoma [mostly non-Hodgkin's lymphoma][165-167]; in the CESAME cohort data, over 40% of the patients that developed lymphoma had EBV-positive tumours.[36] Afif *et al*. reported that 75% of lymphomas in IBD patients were EBV positive[168]. Multiple case reports or small case series of lymphoma following a primary EBV infection in immunosuppressed IBD patients have been published.[169, 170] [171, 172] [173]

An additional rare complication of primary viral infection in immunosuppressed patients is haemophagocytic lymphohistiocytosis [HLH]. Patients with X-linked inhibitor of apoptosis deficiency are at particular risk. In a recent large case series that included 20 paediatric patients, 20% had primary EBV infection.[174, 175]

Despite this concern, there are no comparative or prospective data to support the benefit of routine assessment of EBV serology. Nonetheless, screening for prior EBV infection should be considered in candidates for immunosuppressive therapy, especially thiopurines. In those who test EBV-IgG negative, avoidance of thiopurine therapy should be considered.

In severe cases such as HLH, immunosuppression should be stopped. EBV-positive mucocutaneous ulceration may affect the oropharyngeal mucosa, gastrointestinal tract, and skin and is clearly related to immunosuppressive therapy.[176] [177, 178] [171, 179] [180] Discontinuation of immunosuppression is the primary therapeutic intervention and results in resolution in a high proportion of patients.[177]

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3.5. Influenza Virus – infection and vaccination

Statement 3.13*

Patients on immunosuppressive therapy are considered to have an enhanced risk for development of severe influenza infection [EL5]. Annual influenza vaccination of patients on immunosuppressive therapy is recommended according to national guidelines [EL5]. Live vaccines should not be administered to immunosuppressed patients.

Limited data exist on the epidemiology of influenza infection in patients with IBD. In a large retrospective cohort study that compared the rate and severity of influenza infection in IBD and non-IBD controls, IBD patients had a slightly increased risk of influenza and were more likely to require hospitalization. Steroids were the only medications independently associated with influenza risk.[181] While the incidence of influenza was not greater in IBD patients receiving immunosuppressive therapy[182] during the 2009 H1N1 pandemic, immunosuppression is generally considered to enhance the risk of severe or complicated influenza infection.[183] A retrospective study performed in 12 European IBD centres during the H1N1 pandemic identified 25 patients who developed influenza, of which 88% were immunosuppressed, 28% were hospitalized, and 12% were admitted to the intensive care unit.[184]

According to Centers for Disease Control [CDC] guidelines, annual vaccination is the most effective method for preventing influenza virus infection and is therefore recommended for patients on immunosuppressive therapy. Various vaccine types are available. A live attenuated influenza vaccine should only be used for healthy persons aged 2–49 years and is not recommended for patients on immunosuppression. In contrast, the trivalent/quadrivalent inactivated influenza vaccine may be used for any person older than 6 months, including those on immunosuppressive therapy.[185] Annual vaccination in accordance with national guidelines is recommended, particularly in the post COVID-19 era. Compliance with recommendations remains poor,[186, 187] but uptake of influenza vaccination in CD patients increased between 2005–2012.[188] Vaccination education programs, patient information leaflets, and specialized infectious disease consultations have proven effective in improving uptake of influenza vaccines.[189-191]

There is accumulating data to suggest that influenza vaccination is less effective in patients with IBD receiving immunosuppressants, particularly those receiving combination therapy of an anti-TNF agent and azathioprine.[192-195] The use of anti-TNF agent monotherapy may also reduce response to vaccination.[195-198] The timing of vaccination relative to infliximab infusion does not affect the achievement of serologic protection.[198] The persistence of seroprotection is also lower in patients on anti-TNF agents.[199] The immune response nevertheless remains sufficient to warrant annual vaccination. While baricitinib has limited impact on vaccine response in patients with RA, data are lacking in IBD patients.[200, 201] In a small study, patients receiving vedolizumab had similar vaccine

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responses as healthy controls.[202] Data on influenza vaccine efficacy and use of ustekinumab are lacking.

Various strategies have been developed to optimize influenza vaccination in IBD patients. Temporary methotrexate discontinuation for 2 weeks after vaccination improves immunogenicity in RA patients.[203] Patients on anti-TNF agent monotherapy who received a high-dose influenza vaccine had significantly higher postimmunization antibody levels compared with standard dose,[202] whereas a booster immunization was ineffective in two independent trials.[204, 205] Lastly, influenza vaccination appears safe in patients with IBD and is not associated with a risk of flare.[199, 206]

Statement 3.14*
Immunosuppressive therapy should be **discontinued** in severe cases of varicella infection, disseminated HSV and VZV, symptomatic infectious mononucleosis, EBV-related mucocutaneous ulceration, and severe influenza [EL4]. Immunosuppressive therapy should be **withheld** in cases of measles [EL5].

3.6. Immunosuppressive treatment during viral infections

The severity of reported cases of primary varicella [207] and HSV infection [208-210] strongly support immunosuppressant withdrawal. HZ is one of the most frequent opportunistic infections observed in immunosuppressed IBD patients and is particularly associated with thiopurines and tofacitinib.[21, 211] In severe cases, defined as multi-dermatomal involvement [2 nonadjacent dermatomes, 3–6 adjacent], disseminated [>7 dermatomes], or ophthalmic,[211] immunosuppressants should be discontinued. Temporary or definitive discontinuation of immunosuppressants should be individually evaluated based on IBD characteristics,[21] severity of VZV infection, or recurrence pattern. In patients needing immunosuppression for IBD control, replacement by another agent with lower risk of VZV reactivation and viral infections in general [such as anti-TNF agents] should be considered.[212, 213]

EBV infection is covered in section 3.4.4.

Influenza is generally a self-limited and mild infection in most healthy individuals. IBD patients with influenza have more complications, primarily pneumonia with a higher rate of hospitalization.[214] In severe complicated cases with secondary bacterial pneumonia, acute respiratory distress syndrome, myositis, myocarditis, or multiorgan failure, temporary immunosuppressant withdrawal or transient lengthening of the biologic administration interval until symptom resolution is strongly recommended.

Recent reappearances of measles outbreaks have raised concerns for immunosuppressed IBD patients. The clinical picture can be atypical in these patients and may present without

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rash or fever but may include life-threatening giant-cell pneumonitis or sub-acute measles encephalopathy.[215, 216] Measles also induces a prolonged specific and profound immunosuppression characterised by lymphopenia. This predisposes to potentially fatal opportunistic infections, which account for increased mortality in the months following initial infection.[217] Although cases of measles have yet to be reported in IBD patients on immunosuppressants, it seems reasonable to withdraw them during active infection.

Reintroduction of immunosuppressants and decisions after resolution of viral infection will depend on the competing demands of inflammatory activity, control of IBD, and the risk and severity of reactivation of specific viral infections.

Statement 3.15*
Immunosuppressed IBD patients with an ongoing HSV, VZV, or influenza infection should receive the appropriate antiviral treatment [EL4].

3.7. Antiviral treatment in immunosuppressed IBD patients

Immunocompromised patients with IBD have an increased risk of influenza compared to individuals without IBD [214]. Immunosuppressed IBD patients who contract influenza should receive antiviral treatment with a single neuraminidase inhibitor [oral oseltamivir, inhaled zanamivir, or intravenous peramivir]. This should be commenced as soon as possible. The clinician may consider a longer duration of antiviral treatment than in patients who are not immunosuppressed or have uncomplicated influenza.[214, 218, 219] In the event of exposure to influenza, the need for prompt post-exposure prophylaxis should be considered on a case-by-case basis.

HSV is more common in immunosuppressed IBD patients.[219, 220] There is a dearth of evidence on how to deal with HSV infections in IBD patients. However, data from patients with HIV and transplants suggest that immunocompromised patients with a primary HSV infection should be treated with acyclovir, valacyclovir, or famcyclovir. Intravenous therapy should be considered for patients with encephalitis, herpes dermatitis complicating atopic dermatitis, ocular herpes, and genital disease. Suppressive or episodic treatment should be considered in those with recurrent herpes. The persistence of lesions despite appropriately dosed antiviral therapy in patients with a history of repeated antiviral therapy for recurrent disease should raise suspicion of acyclovir resistance.[221] [222, 223] [224, 225] [226]

Antiviral therapy is recommended for HZ in all immunocompromised patients. The recommended treatment for uncomplicated [typical dermatomal rash] HZ is oral valacyclovir or famcyclovir in higher doses appropriate for VZV. Treatment for complicated [including multi-dermatomal, ophthalmic, visceral, or disseminated] HZ is intravenous acyclovir. Treatment should be prescribed within 72 hours of rash onset and should

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continue for a minimum of 7–10 days. If immunosuppression has been withheld, it may be reasonable to restart after the patient has commenced anti-VZV therapy and the skin vesicles have resolved.[227-231]

3.8. Human Papilloma Virus

Statement 3.16*
Immunosuppressed female IBD patients should undergo annual cervical cancer screening [EL3].

3.8.1. HPV, cervical cancer, and immunosuppression

Several studies have shown that immunosuppressive treatment may increase the risk of persistent HPV infection and ultimately cervical cancer. There is limited data on IBD and HPV. In a cross-sectional study, the HPV 16/18 cervical infection rate was significantly higher in IBD patients than in controls [HPV 16/18 infection rate: 7.3 vs 0.3%; OR: 29.035; 95% CI: 3.64–210.988; $p < 0.001$]. Further analysis revealed that exposure to methotrexate [OR: 4.76; 95% CI: 1.471–15.402; $p < 0.005$] and using more than two types of immunosuppressants [OR: 3.64; 95% CI: 1.255–10.562; $p < 0.013$] significantly increased the risk of high-risk HPV infection. There was no correlation with the use of thiopurines, steroids, or infliximab and the rate of HPV infection [all $p > 0.05$] or with duration of drug treatment.[232] In another study where cervical dysplasia and HPV were reported together for patients with CD, an increased risk was seen for patients receiving immunosuppressants. The overall rate ratio for CD was 1.35 [95% CI: 1.28–1.43]. Compared with CD patients on no treatment, the HR for CD on one immunosuppressant was 1.5 [95% CI: 1.21–2.0] and for two was 1.8 [95% CI: 1.1–3.0].[220]

A meta-analysis using both cervical dysplasia and carcinoma as primary outcome measurements revealed an overall increased risk for cervical dysplasia and cancer [OR: 1.34; 95% CI :1.23–1.46] in IBD patients with current or previous treatment with immunosuppressive medication compared to the general population.[37] Similarly, in a recent prospective study, Li *et al*. observed that all patients who developed cervical neoplasia were receiving immunosuppressants. [233]

Rungue *et al.* observed that the cumulative azathioprine dose is probably associated with cervical cancer, with an 8% increase in the incidence rate ratio [IRR] for high-grade lesions in CD patients [IRR: 1.08; 95% CI: 1.04–1.13]. Cumulative prescription of oral corticosteroids [IRR: 1.02; 95% CI: 0.98–1.06] or anti-TNF agents [IRR: 1.16; 95% CI: 0.87–1.55] had no significant impact on risk.[234] Similarly, Dugué *et al*. demonstrated that azathioprine exposure was associated with a HR 1.4 [95% CI: 0.9–2.1] for cervical cancer; this increased to 2.2 [95% CI: 1.2–3.9] in patients on a high cumulative dose.[235] In another study, patients on various combinations of dual immunosuppression therapy [thiopurines, methotrexate, anti-TNF agents, or corticosteroids] had an OR from 2.04–2.59 for cervical dysplasia; this was greater than the OR of 1.39–2.13 for those on monotherapy.[220]

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Similarly, Singh *et al.* observed that IBD patients treated with either a thiopurine or methotrexate combined with corticosteroids had a 30–40% increased risk of cervical abnormalities.[236] Currently, there are no data on vedolizumab and the occurrence of cervical dysplasia.[237]

3.8.2. Vaccination

Statement 3.17*

Routine prophylactic HPV vaccination is recommended for both young female and male patients with IBD [EL2].

HPV vaccination can prevent >90% of cancers caused by HPV. Types 16 and 18 are the most commonly isolated HPV types in cervical cancer, with type 16 found in approximately 50% of patients with cervical cancer.

Three prophylactic HPV vaccines have been licensed since 2006, including a quadrivalent vaccine [Gardasil ®, Silgard®] containing L1 virus-like particles [VLP] of HPV-6, -11, -16, and -18; a bivalent vaccine [Cervarix®] containing L1 VLP of HPV-16 and -18; and more recently a 9-valent vaccine [Gardasil9®] with L1 VLP of HPV-6, -11, -16, -18, and five additional high-risk types [HPV-31, -33, -45, -52, and -58]. The 9-valent vaccine is currently preferred in national recommendations. Most local guidelines recommend routine HPV vaccination for all males and females aged 11–14 years in a two-dose schedule with catch-up vaccination after this age. The vaccine can be given from 9 years of age. If vaccination starts on or after 15 years of age, three doses should be administered.[238-240] The age limit for catch-up vaccination varies by country. The Advisory Committee on Immunization Practices [ACIP] of the CDC proposes vaccination for all people through 26 years of age.[241] For people of older age [27 –45 years], shared clinical decision making regarding HPV vaccination is recommended for persons with specific behavioural or medical risk factors for HPV infection [including immunosuppression].[241] As an inactivated vaccine, it can be administered to immunocompromised IBD patients. ACIP recommends a three-dose schedule regardless of age for people on immunosuppressants.[241] Few studies have evaluated the immunogenicity or safety of quadrivalent and bivalent vaccines in immunocompromised populations.[242-247] One study was conducted in young females with IBD and showed good immunogenic response without significant vaccine-associated side effects.[242]

3.9. JC Virus

Serologic screening for JC virus before initiating vedolizumab therapy is not recommended in IBD patients. A favourable safety profile was reported based on data in 208 050 patient-years of vedolizumab exposure with only one case of progressive multifocal leukoencephalopathy [PML] in a CD patient with co-existing HIV infection on long-term immunosuppressant therapy. An independent adjudication committee of experts with

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experience in PML and HIV concluded that the most probable cause of PML was the presence of HIV in combination with immunosuppression.[248]

3.10. SARS-CoV-2

Statement 3.18

During the SARS-CoV-2 pandemic, management of IBD should follow usual standards of care [EL-5].

COVID-19 is a new disease with a rapidly evolving evidence base. The risk to IBD patients is still uncertain.

Current real-world experience is tentatively reassuring. Overall, IBD patients do not seem to be at increased risk of either contracting SARS-CoV-2 or developing a more severe disease course. Population studies from China, France, Italy, and Spain have neither identified IBD nor immunosuppressive therapy to be risk factors for disease onset.[249-251] It is likely, however, that many IBD patients modified their behaviour to reduce risk, with several countries promoting shielding.

The second analysis of the SECURE-IBD database included the first 1439 patients submitted to the registry. In addition to age, comorbidity, and disease activity, corticosteroids, thiopurine, or combination therapy with anti-TNF agents and thiopurine and 5-aminosalicylates [5-ASAs] were associated with severe COVID-19, defined as critical care admission or mortality. Anti-TNF agent monotherapy, vedolizumab and ustekinumab did not appear to be associated with severe COVID-19.[252] Anti-TNF agents conferred a protective effect in univariate analysis in this cohort. In an Italian case series, disease activity and UC were also associated with adverse outcomes.[253]

There is a very real risk of disease flare when IBD maintenance therapy is stopped. Accordingly, ECCO promotes the continued management of IBD in line with standard guidelines. We also endorse stringent hand hygiene and social distancing measures as per national recommendations and World Health Organization [WHO]/European Centre for Disease Prevention and Control guidance.

When a disease flare is suspected, SARS-CoV-2 infection should be excluded. This is due to the symptomatic overlap of gastrointestinal manifestations of COVID-19 and IBD flares.[254] In a patient negative for COVID-19, the disease flare should be managed in accordance with standard guidelines as far as resources allow. It is acknowledged that during waves of high COVID-19 prevalence, accessibility of radiology, endoscopy, surgery, infusion clinics, and even monitoring may be considerably reduced. Optimizing IBD care amidst these limitations is discussed in the ECCO-COVID Taskforce paper.[255]

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Statement 3.19

When COVID-19 is clinically suspected, or when a patient tests positive for SARS-CoV-2 [symptomatic or asymptomatic], continuation of 5-ASA and immunosuppressive therapy should be considered on a case-by-case basis according to current knowledge. [EL 4]

At the time of writing, the impact of continuing immunosuppressive therapy and 5-ASA after confirmation of SARS-CoV-2 infection is unknown.

As described in the text for the above statement, registry data are tentatively reassuring for most IBD therapy, with the majority of IBD drugs demonstrating no association with severe COVID-19, as defined by either critical care admission or mortality.[252] The exceptions are prior corticosteroids, thiopurines, combination therapy with anti-TNF agents and thiopurines and possibly 5-ASA. While the SECURE-IBD data records medication use at time of SARS-CoV-2 diagnosis, the impact of continuing immunosuppressive agents after diagnosis of SARS-CoV-2 infection is largely unstudied. With registry data, there is also a risk of bias towards more severe infection in identified cases.

When deciding whether to stop IBD treatment in patients who test positive for SARS-CoV-2, the risks and benefits for the individual patient should be considered. Medications confer a risk of ongoing immunosuppression and pausing therapy may partially restore immune function. However, therapy cessation also predisposes to disease flare, itself a risk factor for severe COVID-19, and immunosuppressive therapy may actually curtail the cytokine storm implicated in acute respiratory distress syndrome. Indeed, dexamethasone is, at the time of writing, the single agent with trial data to support reduction in mortality in COVID-19 patients requiring oxygen therapy, and there are trials of anti-TNF agents in treatment of COVID-19 underway. A further consideration is that if patients are receiving dexamethasone, they may not need their standard immunosuppressive therapy to control IBD for the duration of this treatment.

The individual circumstances of patients with SARS-CoV-2 vary considerably. The virus may be detected in asymptomatic patients in remission, whilst undergoing routine testing prior to a scheduled infusion. At the other extreme, there have been cases of acute severe colitis in those with concurrent COVID-19 infection.[256] For the latter scenario, a Research and Development [RAND] panel-based guidance has been developed.[257] However, as the field is rapidly evolving, it is difficult to provide didactic guidance on each potential scenario. Thus, we recommend a case-by-case approach, with early involvement of both gastroenterologists and infectious disease experts in patients requiring hospital admission.

3.11. COVID-19 vaccination

At present, there are at least 166 vaccines against SARS-CoV-2 at various stages of development,[258, 259] with three phase 3 trials having released significant results.[260-262] The UK launched the first national vaccination program on 8 December 2020,[263] entailing the two-dose mRNA vaccine BNT162b2, a vaccine with response rates of 95% [$p < 0.0001$][260] and a favourable safety profile. The Oxford/Astra-Zeneca COVID-19 vaccine

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uses a replication-deficient chimpanzee adenovirus vector (ChAdOx1) to deliver the full-length SARS-CoV-2 spike protein DNA sequence into the host cell. Vaccination trials for all EMA approved vaccines have demonstrated safety and efficacy in all adult age groups, including both healthy individuals and patients at risk of severe or fatal COVID-19. We tentatively hope that vaccination, coupled with herd immunity, will translate to protection of the most vulnerable and eventually the global return of pre-pandemic life.

Vaccination against SARS-CoV2 has not been directly trialled in the IBD population, or any patients undergoing treatment with immunosuppressive therapy. With mRNA vaccination itself being a novel immunization strategy, the impact of immunosuppression on immunity and vaccine response is uncertain.

As mRNA vaccines as well as the recombinant adenovirus vector vaccines are not live, they are not thought to be of particular risk to patients with IBD. Conversely, the risk of contracting COVID-19 is known to be significant. Accordingly, ECCO supports vaccination against SARS-CoV-2 in the IBD patient population. This view is supported by recommendations from a recent international consensus meeting[264] and the British Society of Gastroenterology (BSG)[265]. As vaccination against SARS-CoV-2 is a rapidly evolving field, we refer for update to the link of the ECCO COVID-19 taskforce https://ecco-ibd.eu/publications/covid-19.html.

4. Mycobacterium tuberculosis

Statement 4.1*

The reactivation risk of latent tuberculosis infection [LTBI] in patients treated with biologics or JAK inhibitors is increased, and the disease can be more severe than in the background population [EL2]. Before its start and, ideally, before any immunosuppression, IBD patients should be screened for LTBI [EL1].

Consider re-screening patients previously exposed to biologicals and JAK inhibitors before switch or swap [EL3]. Under special conditions, re-screening during anti-TNF agent therapy and JAK inhibitors should be considered [EL5].

As tuberculin skin test [TST] and interferon-gamma release assays [IGRA] results are negatively impacted by immunosuppressive therapy, diagnosing latent tuberculosis infection [LTBI] before starting any treatment is advisable.[266-268] Furthermore, exposure to biological therapies appears to be associated with an increased overall risk of tuberculosis [TB] [new diagnosis and reactivation], based on a network meta-analysis [OR: 2.04; 95% CI: 0.71–5.98].[269]

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When compared with placebo, a 4.7-fold increased risk of TB reactivation during anti-TNF agent therapy has been shown in an overall study population in a Cochrane Database Systemic Review.[270]

According to a systematic review in both rheumatologic and non-rheumatologic diseases,[271] the combination of anti-TNF agents with methotrexate or azathioprine results in a 13-fold increased risk of TB reactivation when compared with anti-TNF agent monotherapy.

While there are a few reports of TB reactivation among patients treated with vedolizumab,[22, 272] the available data are insufficient to assess the real risk. Across five trials of ustekinumab-treated patients with psoriasis, no cases of TB reactivation were observed in patients with latent TB receiving concomitant prophylaxis.[273] Indirect comparisons between ustekinumab and anti-TNF agents concluded that the incidence rate of TB was lower among ustekinumab-treated patients than those treated with anti-TNF agents patients [incidence rate: 0.02; 95% CI: 0.00–0.06 vs 0.28; 95% CI: 0.21–0.37 per 100 patient-years, respectively].[274] The risk of reactivation of latent TB in patients with IBD treated with JAK inhibitors is increased. A study in tofacitinib-exposed patients across 48 countries [including 5671 treated patients and 12 664 patient years] found TB as the most common opportunistic infection, with more severe and extrapulmonary TB forms than in the background population.[275]

In patients treated with methotrexate or azathioprine, a short course of corticosteroids, or cyclosporine, several studies showed that the risk of TB is not higher when compared to placebo alone and thus no treatment of LTBI is recommended in these patients.[271, 276, 277] Due to TB cases diagnosed in patients treated with anti-TNF agents despite a negative TB screening prior to anti-TNF therapy,[278, 279] annual re-screening could be considered,[280] especially for patients with a higher TB risk [living or travelling in intermediate or high TB incidence area]. The risk of TB in IBD patients on anti-TNF agents is dependent on the local disease burden of TB.[281] The benefit/risk of preventing reactivation of LTBI should always be considered individually.

4.1. Testing for LBTI

Statement 4.2

LTBI should be diagnosed by a combination of patient clinical data and epidemiological factors, chest X-ray, and TST or IGRA [or both] according to local availability and national recommendations [EL5].

TB evaluation should ideally be considered at diagnosis. If negative or not performed, TB evaluation should be performed prior to initiating any biological or small-molecule therapy. TB evaluation is based on epidemiological risk factors, physical examination, chest X-ray, and TST or IGRA test [or both]. Steroids, immunosuppressive therapy, inflammation, or combinations thereof have a pronounced negative effect on TST and IGRA results in IBD

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patients.[282] Therefore, it is recommended to perform early screening for LTBI at the time of IBD diagnosis,[283] before starting immunosuppressive therapy [or up to 2 weeks after starting], or, failing that, after treatment of the first flare [3 weeks after stopping corticosteroids], preferably with a low inflammatory load. Alternatively, early screening can be performed at any subsequent period in which the patient is in remission.

A diagnosis of [L]TBI should be considered in patients

i) without clinical and radiological evidence of active TB and a positive TST or IGRA test

ii) with negative TST, IGRA, or both but with evidence of previous TB not appropriately treated

iii) with an abnormal chest X-ray suggestive of past and untreated TB [calcification ≥5 mm, pleural thickening, or linear opacities] even if other criteria are absent [284-286]

iv) having a close contact with a bacilliferous patient not followed by TB screening, or in case of a positive screening, without treatment

A positive TST is defined by an induration diameter ≥5 mm. Importantly, skin testing is sensitive but not specific for predicting reactivation of TB; only 5% of immunocompetent persons with a positive test will progress from latent infection to active disease in their lifetime.[287]

Individuals vaccinated with Bacillus Calmette-Guerin [BCG] may react positively to purified protein derivate, resulting in a positive TST.[288, 289] The influence of BCG vaccination is negligible when administered during the first year of life, when the interval between vaccination and TST is >15 years, or in adults >30 years.[290] However, repeated BCG vaccination or exposure to nontuberculous mycobacteria can result in positive TST results.[291] In these conditions, IGRA testing could be more specific.

TST may be negative in patients on corticosteroids for ≥1 month, on thiopurines or methotrexate for ≥3 months, on infliximab, or during active IBD without immunosuppression. Therefore, TST may not be interpretable under these conditions. Consequently, a booster TST might be appropriate for patients on immunosuppressants with a negative TST 1–2 weeks after the first test. In clinical practice, booster TST diagnoses an additional 8–25% of LTBI cases among rheumatologic or IBD patients.[282, 290, 292-295] In theory, repeating TST during immunosuppressive therapy may increase sensitivity for detecting TB at a time when the inflammatory burden is lower. A Spanish prospective cohort study suggested a role for re-screening [after two-step negative TST at baseline], with a single TST after 1 year of therapy to increase the likelihood of detecting LTBI while under therapy,[280] but this strategy requires further validation. Furthermore, in patients with a negative baseline screening who live, travel, or work in endemic TB areas, annual TB testing could be considered while continuing immunosuppressive therapy.[296]

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The following two other diagnostic tests, both IGRAs, are available to screen for TB: QuantiFERON-TB Gold [QFT] and T-SPOT. Both use purified antigens from *M. tuberculosis* to stimulate peripheral-blood lymphocytes to produce interferon-γ. The QFT test measures the amount of interferon-γ in the supernatant of a cell suspension, whereas T-SPOT determines the number of cells producing interferon-γ with the use of an ELISpot assay. IGRAs are more likely to be positive in persons who have recently been infected with *M. tuberculosis*, a group at particularly high risk for disease progression.[297]

Another potential advantage of IGRAs is that there is no cross-reactivity with BCG or with atypical Mycobacteria, except for *M. kansasii, M. marinum*, and *M. szulgai*.[298] Therefore, IGRAs may be particularly valuable in evaluating LTBI status in persons who have received BCG vaccination at younger age. Nine studies including 1309 patients with IBD were investigated in a meta-analysis. The pooled concordance between the TST and IGRAs [QTF and QTF in-Tube] was 85% and the concordance of the TST and TSPOT was 72%,[299] although IGRA sensitivity seems significantly influenced by immunosuppression, similar to TST.[300-302]

Given the low sensitivity of both TST and IGRAs, new diagnostic strategies should be evaluated. Several studies have shown that diagnostic performance for LTBI in IBD improves if an IGRA is used in addition to TST.[303, 304] Therefore, in patients with TB risk factors such as immunosuppressant use and increased risk of progression from infection to disease, a dual strategy based on both TST and IGRA would seem to improve diagnostic yield and could be recommended in countries with medium or high prevalence of TB.[305, 306] Indeed, two recent guidelines and the CDC recommended that a dual strategy of TST and IGRA should be pursued in countries with medium or high TB prevalence.[307, 308]

In case both TST and IGRA are performed, due to limited data on better performance of combining both in non-vaccinated BCG persons,[309] IGRA determination should precede or be concomitant with TST, as TST may increase the production of interferon-γ in IGRA tests.[310]

4.2. Chemoprophylaxis

Statement 4.3

Patients diagnosed with LTBI prior to biological or small-molecule therapy or prolonged high-dose systemic steroids should be treated with a complete therapeutic regimen for LTBI [EL1]. In other situations, specialist advice should be sought. When there is LTBI and active IBD, biological or small-molecule therapy should be delayed for at least 4 weeks after chemotherapy, except in cases of greater clinical urgency and with specialist advice [EL5].

Chemotherapy for LTBI may vary depending on regimen. The classical TB chemoprophylaxis regimen is based on isoniazid [INH] for 6–9 months [Table 2]. [284, 311-313] Randomized trials have shown that INH provides approximately 90% protection against TB after

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completion of a 9-month course, and 60–80% protection after a 6-month course.[314] However, the regimen is associated with poor adherence and toxicity. More recently, two open-label randomized non-inferiority trials demonstrated non-inferiority to the classic daily 9-month regimen of INH for the prevention of active TB. One compared 3 months of directly observed once-weekly therapy with rifapentine plus INH [combination-therapy group] in subjects at high risk for TB but not exposed to immunosuppressive therapy.[315] The other trial compared a 4-month regimen of rifampicin. Both trials revealed better adherence when compared to the standard regimen.[316] INH-related hepatotoxicity occurs in approximately 0.15% of patients, may occasionally be severe and life-threatening, and is unrelated to dose or blood concentration.[317] Hence, it is advisable to monitor liver function at regular intervals, with cessation or alteration of therapy if transaminases exceed 3-fold above upper limit of normal associated with hepatitis symptoms or jaundice, or 5-fold in the absence of symptoms.[293, 311, 318-320]

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Table 2 – Tuberculosis chemoprophylaxis regimens

Drug[s]	Posology	Duration [months]	Estimated Protection	Observations	References
INH	300 mg/day; maximum [5 mg/kg]	6–9	9 months: 90% 6 months: 60–80%	Poor adherence associated with toxicity; vitamin B6 [300 mg/ week] is recommendedy to reduce neurotoxicity	[284, 311-314, 321]
Rifapentine +INH	Rifapentine 900 mg plus INH 900 mg once weekly; 12 doses	3	Not inferior to INH 9 months	Better adherence	[315]
Rifampicin	600 mg/day; maximum [10 mg/Kg]	4	Not inferior to INH 9 months	Better safety and adherence	[316]

No prospective or controlled data are available on the ideal timing of starting biological or small-molecule therapy once TB treatment has begun. In case of active TB, biological or small-molecule therapy should be delayed at least for 2 months after anti-tuberculosis treatment with full compliance has begun, and until the drug-susceptibility profile of *M. tuberculosis* in those with positive cultures is known.[322] In case of LTBI, immunosuppressive therapy should be avoided for at least 1 month after TB treatment has begun. Thiopurines may be continued during treatment of TB, although studies are warranted to address both the infectious and hepatotoxicity risk. Importantly, positive TST or IGRA may remain positive after successful TB therapy;[323] thus patients should be closely monitored clinically given the minor risk of evolution towards active TB.

5. Bacterial infections

5.1. *Streptococcus pneumoniae* infection and vaccination

Patients with IBD have an increased risk of pneumococcal infection and a 2- to 3-fold higher risk of invasive pneumococcal disease [meningitis and bacteraemia] even in the 5 years preceding IBD diagnosis when patients were treatment free, suggesting a vulnerability inherent to the underlying disease.[324] One of the most prevalent infections in immunosuppressed patients with IBD is bacterial pneumonia.[19, 325] The 1-year mortality is lower in patients with IBD vaccinated against pneumococcus [2.1%] compared with those not vaccinated [4.5%].[326]

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Statement 5.1*

Pneumococcal vaccination should be recommended for all patients with IBD [EL3].

Two pneumococcal vaccines are now available: the 23-valent pneumococcal polysaccharide vaccine [PPSV23] and the 13-valent pneumococcal conjugate vaccine [PCV13]. Stepwise pneumococcal vaccination, namely a PCV13 prime-PPSV23 boost strategy, with an interval of at least 8 weeks between the two vaccinations, is now endorsed based on the CDC and the European Society of Clinical Microbiology and Infectious Diseases recommendations for young children, adults >65 years, and patients at risk for pneumococcal disease. In patients with CD, there was no general difference in the persistence of antibodies 1 year after vaccination with either PPSV23 or PCV13 as measured by serotype-specific IgG or functional antibodies. However, patients treated with immunosuppressive drugs in combination with anti-TNF agents had impaired immune persistence against both PPSV23 and PCV13.[327] The same was observed in two independent cohorts for PPSV23.[328, 329] Among patients starting tofacitinib, diminished responsiveness to PPSV23 but not influenza vaccination was observed, particularly in those taking concomitant methotrexate. Long-term treatment [≥3 years] with ustekinumab does not compromise the immune response to T cell-dependent or -independent vaccines [response to pneumococcal or tetanus toxoid vaccinations] in patients with moderate-to-severe psoriasis.[330] One study showed that PCV13 was more immunogenic than PPSV23 after 4 weeks.[331] Overall, the administration of PCV13 was highly immunogenic. However, a slightly lower seroprotection rate was observed in those using anti-TNF agents.[332]

5.2. *Legionella pneumophila* infection

Statement 5.2*

Patients with IBD on immunosuppressive therapy with pneumonia should be tested for *Legionella pneumophila* [EL4]. In case of *Legionella pneumophila* infection, immunosuppressive agents should be temporarily withheld until resolution of active infection [EL5]

No vaccine is available and effective chemoprophylaxis for *Legionella pneumophila* has not been described. The key to diagnosis is appropriate sputum microbiological culture and real-time PCR on respiratory samples.[333] PCR provides results within a short time frame, but its access may be limited. Antigen detection in urine [detects only *L. pneumophila* serogroup 1; this accounts for 70–80% of cases] can be easily performed. Direct fluorescent staining on respiratory specimens has a sensitivity ranging from 25–75%. Real-time PCR on urine and serum is not more sensitive than culture.[334] Serological testing is also available; a 4-fold increase in titre between the acute and convalescent titre is required for a definitive serologic diagnosis. *Legionella*-directed antibiotics, such as macrolides and respiratory fluoroquinolones, are not always included as first-line treatment for pneumonia and should be considered in immunocompromised patients with pneumonia.

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Immunosuppressive therapy is considered to confer a high risk for infection with *L. pneumophila*.[335] Exposure to anti-TNF agents is a major risk factor for development of *L. pneumophila* infection, which should be excluded in all cases of pneumonia.[336] Invasive *L. pneumophila* infections, some with fatal outcome, have been reported in patients on immunomodulators for IBD or rheumatological conditions.[337, 338] Fulminant legionellosis and *L. pneumophila* pneumonia in pregnant patients treated with anti-TNF agents for CD has also been reported. In most of these cases, infection occurred early within the first year of immunomodulator or anti-TNF agent treatment. One case of infection with *L. pneumophila* in a patient exposed to ustekinumab monotherapy has been reported, while a few other cases have been reported during the development program of vedolizumab and tofacitinib.[339]

5.3. *Salmonella* and *Listeria* infection

Statement 5.3*

Patients receiving immunosuppressive agents are at risk of more severe infections with *Salmonella enteritidis* and *S. typhimurium* [EL4] and systemic and central neurological infections with *Listeria monocytogenes.*[EL4] The incidence of *L. monocytogenes* infections appears higher in patients treated with anti-TNF agents compared with other immunosuppressive agents [EL4]. Immunosuppressive therapy should be temporarily withheld until resolution of the active infection [EL5].

For IBD patients, invasive *Salmonella spp*. infections related to immunosuppressive therapy have been reported.[340-350] Definitive diagnosis is made by isolating *Salmonella spp.* from blood, stool, or urine. Salmonellosis is treated with antibiotics such as fluoroquinolones or third-generation cephalosporins. In cases of *S. typhimurium* osteomyelitis,[351] aortitis,[352] or septic arthritis,[353, 354] a combination of antibiotics and surgical treatment may be required. Immunosuppressants should be temporarily withheld until resolution of active infection. Immunosuppressive therapy is considered to confer a high risk for intestinal or systemic *Salmonella spp*. infections.[355-358]

Immunosuppressive therapy is considered to confer a high risk for *L. monocytogenes* infection, which causes primarily severe septicaemia and meningitis accompanied with considerable mortality.[359] Compared with other immunosuppressants, anti-TNF agents appear to confer a particular risk for serious infection.[340, 360-374] Given that *L. monocytogenes* infections after infliximab treatment frequently occur after three or fewer infusions, reactivation of latent infection could be considered. Treatment for *L. monocytogenes* consists of ampicillin, amoxicillin, or case of allergy to penicillin, trimethoprim/sulfamethoxazole [TMP-SMX].

Prevention of *Salmonella spp*. and *L. monocytogenes* infections consists of food hygiene and careful food choices [such as avoidance of raw eggs, unpasteurized milk, raw-milk cheese, and insufficiently cooked or raw meat].

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Diagnosis is made by appropriate microbiological blood and cerebrospinal fluid gram staining and cultures. A high index of suspicion is appropriate for patients on immunosuppressive therapy who present with signs and symptoms of meningitis or other neurological symptoms. Comprehensive investigation, including lumbar puncture, should be performed as soon as such symptoms develop.[366] This may lead to early diagnosis and treatment, which is important given the pathogenicity of *L. monocytogenes*. No conclusive data are available on whether immunosuppressive should be temporarily or indefinitely withheld in the event of active infection. Nevertheless, there are some reports of reinstitution of immunosuppression after treatment of active infection.[360]

5.4. *Clostridioides difficile* infection

5.4.1. When to perform screening

Statement 5.4*

Screening for *C. difficile* infection [CDI] is recommended at every disease flare in patients with IBD and especially in patients receiving immunosuppressive therapy [EL3].

IBD is an independent risk factor for *C. difficile* [formerly *Clostridium difficile*] infection, even in the absence of traditional risk factors such as antibiotic exposure and hospitalization. A meta-analysis including 12 studies reported a significant association between community-acquired CDI and IBD [OR 3.72],[375] which was also observed in paediatric patients.[376] A population-based study revealed that patients with IBD were approximately five times more likely to develop CDI than patients without IBD [HR 4.79], with no differences between UC and CD.[377] Patients with colonic involvement seem more likely to develop CDI [OR 2.76],[378] although the risk of CDI infection [7%] is not negligible in IBD patients without colon involvement.[379] CDI is significantly more frequent in IBD patients experiencing flares than in both inactive IBD and non-IBD groups [28.8% vs 5.6% vs 0%, respectively; $p = 0.001$].[380]

Conflicting evidence exists on the impact of immunosuppressive drugs on CDI risk in IBD. A recent meta-analysis concluded that there is indeed a significant association between use of biologics [mainly anti-TNF agents] and CDI [OR 1.65]. Conversely, there was no association with 5-ASA or immunosuppressant use.[378] However, a subsequent study reported that steroids [HR 2.54] and infliximab or adalimumab [HR 2.69] were associated with an increased risk of CDI,[377] which was confirmed in an independent cohort.[380] Limited data are currently available for vedolizumab, although a post-hoc analysis from phase 2 and 3 trials revealed that all CDIs occurred in the vedolizumab group.[22]

CDI negatively impacts short- and long-term IBD-related outcomes, including colectomy and mortality rates. CDI also results in longer hospitalizations, escalation in IBD therapy, increased readmission rates, and increased in-hospital expenditures in adult[381, 382] and paediatric[376, 383] IBD patients. A meta-analysis revealed significantly higher long-term colectomy risk [OR: 2.22] and significantly higher short-term [OR 3.84] and long-term [OR 3.65] mortality for IBD patients with concurrent CDI.[378] A later study confirmed that CDI

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increased mortality among patients with IBD [HR 2.28].[377] In mild IBD flares with rapid response to treatment, screening for CDI may not be necessary.

5.4.2. CDI screening

Statement 5.5

Diagnosis of CDI requires documentation of toxigenic *C. difficile* in stool accompanied with diarrhoea. A two-step algorithm with a highly sensitive test such as glutamate dehydrogenase [GDH] antigen enzyme immunoassay or nucleic acid amplification *tests* should be used initially, followed by a second test with high specificity, such as toxin A/B enzyme immunoassays [EL3].

The diagnosis of CDI requires detection of the presence of toxigenic *C. difficile* in stool along with a compatible clinical syndrome, including diarrhoea.[384] Hence, laboratory rejection of formed stool specimens submitted for testing could be considered. As an exception, for IBD patients with suspect CDI who had ileus, a rectal swab can be used with adequate sensitivity and specificity. Patients with suspected CDI should be placed on pre-emptive contact precautions pending *C. difficile* test results, and if positive, continue contact precautions for at least 48 hours after diarrhoea has resolved. In routine clinical practice, several different laboratory tests can be used to diagnose CDI. Some tests detect the presence of toxins in stool, such as enzyme immunoassays [EIA] and the cytotoxicity neutralization assay [CCNA]. Recently, ultrasensitive toxin immunoassays have been developed that are up to three orders of magnitude more sensitive than EIAs.[385] Other tests target the organism itself, such as GDH antigen assays or cultures for the presence of *C. difficile* that can produce toxins in vitro [toxigenic culture]. Finally, molecular methods, such as nucleic acid amplification technology [NAAT] tests, detect the presence of the toxin genes.[386] Some authors now recommend use of a single-step, highly sensitive NAAT instead of EIAs that test for toxins or multistep testing for *C. difficile* bacterial products or genes.[384, 387] However, the limited PPV and high cost limit the use of NAAT as a stand-alone test. Therefore, since no single test is suitable as a stand-alone test, some European guidelines recommended a two-step algorithm to optimize CDI diagnosis.[388] A test with a high NPV [highly sensitive test], such as GDH EIA or NAAT, should be used as a first test, followed by a second test with a high PPV [highly specific test], such as toxin A/B EIAs. Samples with a negative first test result can be reported as negative. Patients with a confirmatory positive second test result can reliably be classified as having CDI.[388] An alternative algorithm is to test simultaneously with both a GDH and toxin A/B EIA. CDI is likely to be present if both tests are positive. In samples that are GDH positive but toxin negative, NAAT should be used as second test.[388]

Although there are numerous commercially available EIAs for both toxins A and B with good specificity, insufficient sensitivity precludes their use as a diagnostic modality.[389, 390] Moreover, EIAs designed to detect only toxin A are likely to underreport CDI, as toxin A-negative *C. difficile* strains account for up to 3% of CDI. EIAs for *C. difficile* GDH showed high sensitivity and can be useful as initial screening in a multistep diagnostic approach.[386,

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388, 389] However, the GDH assay has low specificity since it can detect *C. difficile* strains that do not produce toxin. By amplifying the *C. difficile* toxin B gene, NAAT technology could be used with high sensitivity and specificity.[391, 392] Given its high sensitivity and the potential for false-positive results, the NAAT test has been suggested in algorithms together with EIAs.[386, 388] CCNA for *C. difficile* toxin B still represents the diagnostic gold standard.[393] Toxigenic culture, based on detection of toxin production after isolation in culture, has increased sensitivity over CCNA and can be used as an alternative.[394] However, these reference methods are not considered practical, due to the lengthy turnaround time [24–48 hours] and requirements for special laboratory experience. Interestingly, a recent retrospective study suggested that toxin+ IBD patients compared to toxin- PCR+ IBD patients had a significantly higher response rate to antibiotics and lower chances of requiring IBD therapy escalation.[395]

Endoscopy is not recommended as a diagnostic tool for CDI as pseudomembranes are rarely found and their absence does not exclude infection.[396] Pseudomembranes were only reported in 13% of hospitalized IBD patients with CDI, a finding that was independent of immunosuppressant use.[397]

5.4.3. Treatment of *C. difficile* infection

Statement 5.6*

Oral vancomycin and fidaxomicin for 10 days are equally effective in treating non-severe CDI [EL1]. For severe CDI, intravenous metronidazole should be added to oral vancomycin for 10 days [EL3].

Treatment of CDI recurrence includes oral vancomycin, fidaxomicin, faecal microbiota transplantation [EL3], and bezlotoxumab [EL5].

In CDI, use of immunosuppressants can be maintained after careful risk-benefit evaluation and clinical judgement [EL5].

Two recent RCTs concluded that oral vancomycin was superior to metronidazole in terms of clinical cure of a first episode of CDI.[398, 399] [Table 3]. Fidaxomicin, a narrow-spectrum antibiotic introduced in 2011, is noninferior to vancomycin for clinical response to a first episode of CDI.[400, 401] It has not been determined if this applies to patients with IBD. As vancomycin and fidaxomicin may not be easily available in outpatient settings, oral metronidazole can be used in settings where access to vancomycin or fidaxomicin is limited.[402]

CDI is associated with an increased risk of multiple adverse outcomes in IBD [see section 5.4.1]. Asymptomatic shedding of *C. difficile* spores can continue for weeks following resolution of symptoms. Thus, treatment response should be based only on clinical assessment in non-IBD patients. However, in patients with IBD, symptoms related to CDI may overlap symptoms related to IBD flares, and thus creates diagnostic challenges when assessing for CDI treatment failure. In this setting, repeated testing in patients with ongoing

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diarrhoea under CDI treatment may be considered to guide management, despite risk of false-positive results.

In case of recurrent CDI, the use of a tapered or pulsed treatment regimen with vancomycin has been proposed.[402] Fidaxomicin was shown to be non-inferior to vancomycin in patients with a first recurrence of CDI, and can be used especially in patients initially treated with vancomycin.[403] Other antibiotics, such as rifaximin, may be considered in case of recurrent disease.[402] Faecal microbiota transplantation [FMT] is recommended in case of multiple recurrences of CDI.[402, 404] Prevention of CDI recurrence following FMT ranges from 70–90% in both observational and randomized clinical trials in patients without IBD,[405] with similar rates in patients with IBD.[406] Use of FMT has also been reported in some specific settings, such as patients with CDI and ileal pouch anal anastomosis.[407] Further studies are required to determine the optimal regimen and indication of FMT in the setting of active IBD.

Although recurrent CDI has been effectively treated by *Saccharomyces boulardii*, the evidence is still insufficient to recommend probiotics.[408] Bezlotoxumab, a monoclonal antibody against *C. difficile* toxin B, reduced rates of recurrent CDI compared to placebo in non-IBD patients receiving antibiotic treatment for CDI.[409]

Thiopurines and anti-TNF agents have been variously associated with an increased risk of CDI in observational studies,[380, 410] although IBD disease activity as a confounding factor may be difficult to fully control in this setting. In a pooled analysis of clinical trials data, 34 cases of CDI were reported in patients exposed to vedolizumab [incidence rates per 1000 person-years: 7.0, 95%: CI 1–5] versus 0 cases in patients exposed to placebo. Further studies are required to assess the impact of vedolizumab on the risk of CDI. The impact of immunosuppressants on CDI course remains unclear. In patients with current CDI, the maintenance of immunosuppressive therapy should be carefully considered based on risk-benefit evaluation and clinical judgement.

Table 3 Treatment options for *C. difficile* colitis

	Treatment options*	**Observations**
Initial episode [10 days of therapy]	VAN 125 mg orally 4 times daily OR FDX 200 mg orally twice daily OR metronidazole, orally 500 mg 3 times daily	 FDX less readily available than VAN if above drugs not available
Initial, fulminant [hypotension or	VAN, 500 mg 4 times daily [by mouth, nasogastric tube, or rectal] PLUS	if ileus: consider adding rectal instillation of VAN [retention enema: 500 mg

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shock, ileus, megacolon]	intravenous metronidazole [500 mg every 8 hours]	in 100 cc, 4 times daily]
First recurrence	VAN 125 mg orally 4 times daily for 10 days OR prolonged tapered and pulsed VAN regimen [e.g. 125 mg 4 times daily for 10–14 days, 2 times daily for a week, once daily for a week, and then every 2 or 3 days for 2–8 weeks] OR FDX 200 mg twice daily for 10 days	if metronidazole was used for the initial episode if VAN was used for the initial episode if VAN was used for the initial episode
Second and subsequent recurrence	VAN in a tapered and pulsed regimen OR VAN 125 mg orally 4 times for 10 days followed by rifaximin 400 mg 3 times daily for 20 days OR FDX 200 mg twice daily for 10 days OR Faecal microbiota transplantation	

*adapted from Clinical Practice Guidelines for *C. difficile* Infection, 2017 Update from IDSA and SHEA[402]

VAN, vancomycin; FDX, fidaxomicin

5.5. Nocardia infection

Statement 5.7

Patients receiving immunosuppressive therapy are at risk of systemic and cutaneous infections with *Nocardia spp*, particularly when treated with corticosteroids [EL4]. Although *Nocardia spp* is a ubiquitous agent, the risk in IBD patients is low [EL5].

Background: See supplementary material.

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5.6. Meningococcal infection

Statement 5.8

Meningococcal vaccination should be administered to patients with IBD as per regional or national recommendations for the general population [EL5].

Systematic meningococcal vaccinations are not currently recommended for adults with IBD under immunosuppressive therapy with no risk factors for meningococcal disease, as data are lacking to support an increased risk in that population. Routine childhood meningococcal vaccination is recommended in most countries with booster doses in high-risk individuals.

The epidemiology of meningococcal disease is dynamic and all serogroups vary temporally and geographically.[417] Different vaccines against different serogroups are available [Men-C, Men-C-ACYW, and Men-B], and country-specific immunization guides have been adopted based on local epidemiology.[418-420]

Meningococcal vaccination is recommended in persons at a higher risk for invasive meningococcal disease due to underlying medical conditions [e.g. anatomic or functional asplenia, sickle cell disease, HIV infection, persistent complement component deficiency, including patients using a complement inhibitor] and those at risk due to exposure [e.g. travellers to countries with hyperendemic or epidemic meningococcal disease, microbiologists routinely exposed to *Neisseria meningitidis* isolates, military recruits, and college students in residential housing.[418, 419]

IBD may be associated with hyposplenism, which has been shown to be more frequent in UC than in CD.[421-425] Hyposplenism may be associated with colonic IBD, which is transient and related to the severity and extension of colitis.[423, 424] However, there is no recommendation to systematically screen for splenic dysfunction in patients with IBD; therefore, the population who would benefit from meningococcal vaccination is unknown.

Two cases of meningococcal disease have been reported in patients with CD on anti-TNF agents.[426, 427] The first case was meningococcal meningoencephalitis in a 51-year-old female with CD treated with certolizumab pegol for 6 months [dosage and concomitant immunosuppression unspecified].[426] The second was subacute meningococcaemia secondary to *N. meningitidis* in a 59-year-old female with CD on adalimumab monotherapy for 14 months at a dose 40 mg per week.[427] Both patients were treated with ceftriaxone and recovered uneventfully. The authors did not mention the presence or absence of hyposplenism in their reports, which could have been a risk factor for meningococcal disease.

The overall risk of meningitis in IBD patients was evaluated for the first time in a retrospective cohort study using an insurance database from 2001 to 2016. They identified 50 029 patients with CD and 59 830 patients with UC matched to 296 801 non-IBD comparators. The incidence of claims for meningitis requiring emergency visit or hospitalization was 27.6/100 000 person-years for those with CD, 20.7/100 000 person-years for those with UC and 12.7/100 000 person-years for matched comparators. CD

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patients had an IRR of 2.17 [95% CI: 1.69–2.78] and UC patients had an IRR 1.63 [95% CI: 1.26–2.11] compared with matched non-IBD comparators.[428] In a nested case-control study within the cohort, the association of meningitis claims with comorbidities and medications used to treat IBD was evaluated. The data source did not allow for precise identification of meningitis subtypes. The aetiology of meningitis cases was bacterial in 25% and 23% of the IBD and non-IBD cohort, respectively, but specific causal pathogens could not be identified. IBD patients who were treated with oral 5-ASA had a significantly lower odds ratio [OR: 0.40; 95% CI: 0.26–0.62] of having a claim for meningitis but no significant association with other IBD drugs was shown. Most patients did not receive immunosuppressive therapy. Younger age categories had a higher rate of meningitis.[428]

This study had limitations, including a selection bias. The median age of cases was approximately 55 years in the cohort and does not support the author's recommendations of general meningococcal vaccination in young IBD patients. The very small sample size of patients exposed to IBD drugs did not provide the statistical power to assess the effect of these drugs on susceptibility to infection. The authors were not able to adjust for disease severity or meningitis risk factors, which may have introduced bias. More studies are needed to determine if IBD patients have a higher risk of *N. meningitidis* meningitis.

6. Parasitic and fungal infections

Statement 6.1

The risk of fungal infection in IBD is low. Systemic infections are exceptional, but mortality is high [EL4]. Apart from *Pneumocystis jirovecii,* chemoprophylaxis is not indicated. Chemoprophylaxis following systemic fungal infection should be discussed with an infectious disease specialist [EL5].

Statement 6.2

Screening for parasitic or fungal infections should be considered in residents of endemic areas or with relevant travel history [EL5].

Background: See supplementary material.

6.1. *Pneumocystis jirovecii* infection

Statement 6.3

For patients with IBD on triple immunosuppressive therapy [including steroids, methotrexate, thiopurines, biologicals], standard prophylaxis with TMP-SMX should be strongly considered [EL4]. For those on double immunosuppressive therapy, prophylactic TMP-SMX may also be considered, especially if one of these is a calcineurin inhibitor [EL4]. TMP-SMX should also be considered for any combination of high-dose corticosteroids, low lymphocyte count, or JAK inhibitors [EL5].

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Background: See supplementary material.

7. Special situations

7.1. Patients travelling frequently or travelling to developing countries

7.1.1. Pre-travel vaccination

7.1.2. Risk of disease flares after travel-related enteric infections and evaluation of returning travellers

Statement 7.2
Patients with IBD, including those on immunosuppressive therapy, do not appear to be at increased risk for acquiring malaria or for a more severe disease course and should follow standard guidelines for prevention [EL5].

Background: See supplementary material.

7.2. Infectious diarrhoea in immunosuppressed IBD patients

Background: See supplementary material.

7.3. Malaria

Background: See supplementary material.

Statement 7.1*
Given the lack of data, it is currently not possible to advise against travelling to countries with increased infection rates. However, pre-travel counselling regarding safety measures is strongly recommended for patients under immunosuppression travelling to endemic areas. [EL4] Specific travel recommendations from national authorities and the World Health Organization should be consulted [EL5].

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7.4. Probiotics in patients on immunosuppressive therapy

Statement 7.3
Intake of probiotics in patients receiving anti-TNF agents is probably safe, but safety may be a concern for probiotics with beta-haemolytic activity [EL5].

Background: See supplementary material.

8. Vaccination and safety screening before starting immunosuppressive treatment

8.1 General aspects

Despite the increased risk of infections, several studies have shown that patients with IBD are not vaccinated appropriately.[486-488] The immunization status of IBD patients should be markedly improved. In this guideline, an overview of a routine vaccination program and an IBD-specific program that is relevant for each patient will be presented [Table 10]. Specific vaccination in patients with IBD is discussed in the different sections in this guideline that address specific viral and bacterial pathogens. As immunization programs may differ between countries, it is highly recommended to match current statements with national guidelines. In this section, we provide an overview on vaccination schedules in IBD patients with recognition of variations in regional practices, including vaccinations against infections thought to be of particular risk to IBD patients, and the use of live vaccines in IBD.

A few general aspects should be considered (adopted and modified from [489]):

- The individualized vaccination program should be explained to the patient by the IBD specialist, thus providing a basis for shared decision making. The program should be jointly implemented by the primary care physician, the IBD team, and the patient.
- Checking vaccination status, early during disease, and then in yearly intervals is recommended in particular for IBD specific vaccination requirements
- There is no evidence that vaccination in IBD patients induces a flare
- The success of immunization may be impaired by immunosuppression [e.g. HBV, check anti-HBs titre]
- The vaccine should preferably be administered during quiescent disease, if possible before starting immunosuppression
- If vaccination is to be administered during immunosuppression, use the period of lowest immunosuppression [consider elimination half-life of the drug]
- Vaccination of close contacts is a highly important ‘cocoon strategy’
- Live vaccination is generally considered unsafe during immunosuppression

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8.2 Live vaccines in the immunocompromised host

Statement 8.1*

Live vaccines in patients with IBD receiving immunosuppressive therapy are generally considered unsafe. It is recommended to wait for at least 1–6 months after termination of immunosuppressive therapy before administration of a live vaccine [EL5].

The decision to administer any live vaccine should be considered on a case-by-case basis [EL5]

There is limited clinical data to support the safe use of live vaccines in patients receiving immunosuppressive therapy and existing guidelines are largely based on expert opinion. The Infectious Diseases of America/CDC,[490] UK Green Book [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/655225/Greenbook_chapter_6.pdf [accessed 7 November 2020], and the European League Against Rheumatism [EULAR][489] suggest that live vaccination may be safe during low-dose immunosuppression [see Table 1 for definition]. This chapter summarizes the evidence by vaccine, where not covered elsewhere in the text, and thereafter provides an overview of specific recommendations.

Live vaccination in newborns against BCG and rotavirus are covered in section 8.5.

8.2.1 Varicella and Herpes zoster [HZV]

ZVL is safe and effective in patients receiving thiopurines, methotrexate,[93, 95] and even anti-TNF agents.[94, 491, 492] These patients will have had some pre-existing immunity from prior VZV infection or varicella vaccination. A large RCT studying the safety, long-term immune response, and effectiveness of ZVL in patients using anti-TNF agents across disease indications [VERVE trial; clinicaltrials.gov: NCT02538341] is ongoing. As of November 2019, 617 patients have been recruited at 33 centres. By week 6, there were no confirmed cases of disseminated or local VZV infection or shingles reactivation. Nevertheless, as stated in recommendation 3.8, RZV, if available, is the preferred vaccine for all patients. The relative safety and efficacy of varicella vaccination in children with IBD receiving immunosuppressive therapy has been shown.[493] Refer to section 3.4.2 for further details.

8.2.2 Yellow fever

Experience is based on the benign post-vaccination course observed after inadvertent yellow fever vaccination [494, 495], with some cases demonstrating adequate immunoprotection.[494-496] A recent prospective multicentre controlled observational Swiss study revealed that 15 immunosuppressed travellers given yellow fever vaccine while on low-dose methotrexate [20 mg/week or less] responded serologically with no serious reactions.[497]

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8.2.3 Measles

One case of a safe and successful measles vaccination in a CD patient receiving vedolizumab and methotrexate has been reported. However, methotrexate was stopped 2 weeks before and restarted 4 weeks after vaccination in this patient.[498]

Documentation of vaccination with two doses of the live attenuated measles vaccine is recommended as an adequate measure to verify immunity.[499] Vaccinated immunocompromised IBD patients have similar antibody titres as the general population.[500] Documented immunization supersedes serologic screening, as false-negative results are common. Measles vaccination elicits a humoral and cell-mediated immune response, which leads to lower antibody titres compared with natural infection.[499] Serologic screening is recommended if documentation of vaccination is not feasible. Immunosuppressed individuals who are susceptible require post-exposure prophylaxis in the event of measles exposure.

8.3 Scheduling live vaccination in IBD

Ideally, live vaccines should be administered prior to initiation of immunosuppressive therapy. Likewise, when therapy has been interrupted to facilitate administration of live vaccines, immunosuppression should not be recommenced until after a safe interval has elapsed. In either situation, a minimum interval of 3–4 weeks is sufficient to cover the incubation period and clearance of vaccine virus [Table 9].

A systematic review of 64 studies of vaccination in immunosuppressed populations demonstrated that adverse events following live vaccination are relatively rare.[501] However, there is still a lack of conclusive evidence to support routine live vaccination in the IBD patient on immunosuppressive therapy. The decision to vaccinate should be guided by individual risk assessment, defining the circumstances in which there is a potential benefit of receiving live vaccines, and after discussing the benefits and risks with the patient and as part of a multidisciplinary team.

Immunization of close-contacts [‘cocoon strategy’] is an important means of protecting immunosuppressed patients.[502] The MMR, live varicella, ZVL, and rotavirus vaccines can be safely administered to household contacts of immunosuppressed individuals, as transmission to contacts does not occur or can be minimized by simple precautions [Green book Chapter 6].[503] Likewise, close contacts should also be vaccinated annually against influenza with the age-appropriate vaccine, as transmission of live influenza vaccine virus is only a concern for very severely immunocompromised patients requiring isolation. While rarely used, vaccination of close contacts with live smallpox and oral polio vaccines would pose a significant risk for immunosuppressed IBD patients.[490, 504]

Interruption of immunosuppressive therapy has long been recommended to facilitate the safe administration of live vaccines. In longstanding UK Guidance, an interval of 3 months is recommended following discontinuation of high-dose steroids, thiopurines, and

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methotrexate and 6 months for other immunosuppressants [e.g. chemotherapy, anti-rejection drugs, Green Book Chapter 6].[503]

While comprehensive data are not available to support shorter intervals for the many agents involved, an alternative approach advocates intervals based on the pharmacokinetic and pharmacodynamic data of the drug.[505] Both drug elimination and immune reconstitution influence safety. A rule of thumb is to use 5 times the elimination half-life of a drug, as there are no significant concentrations of a medication after this period.[505] This is a strategy also used by other guidelines addressing this issue.[505]. After live vaccination, it is recommended to wait at least 3–4 weeks [given the incubation period of 7–21 days for measles]. Based on these estimates, Table 9 presents the minimal intervals between stopping immunosuppressive therapy and administration of live vaccines.

Table 9: Suggested timeframe between stopping immunosuppressants and live vaccination, considering drug elimination half-life [2, 505-509]

Drug	**Elimination half-life**	**Stopping before live vaccines**	**Restart after live vaccines**
Steroids [prednisone] >1 mg/kg, >14 days [children] >20 mg/day, >14 days [adults]	2–3 hours	1 month	1 month
Thiopurines$^{\alpha}$ [azathioprine and 6-MP$^{\beta}$: approximately 2 hours]	Several days [6-TGN$^{\delta}$]	3 months	1 month
Methotrexate, low dose [adults]	3–10 hours	1 month	1 month
Tofacitinib	3 hours	1 month	1 month
Infliximab	7-12 days	3 months	1 month
Adalimumab	approximately 2 weeks	3 months	1 month
Golimumab	approximately 2 weeks	3 months	1 month
Certolizumab	approximately 2 weeks	3 months	1 month
Cyclosporine$^{\gamma*}$	8.4 hours [10–27]	1 month	1 month
Tacrolimus*	23–46 hours	1 month	1 month
Vedolizumab**	25 days	3–4 months	1 month
Ustekinumab	approximately 19 days	3 months	1 month

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[α]ZVL administration is considered safe with low-dose methotrexate [≤0.4 mg/kg/week] and azathioprine [≤3.0 mg/kg/day] or 6-mercaptopurine [≤1.5 mg/kg/day]; [β]6-MP: 6-mercaptopurine; [δ]6-TGN: 6-thioguanine nucleotides; [γ]Cyclosporine modified.

*Immediate-release formulations

**Vedolizumab is gut selective. While the period of 3–4 months for stopping the drug before administration of a live vaccine may be lengthy, further information is currently unavailable. The stopping period should be discussed on a case-by-case basis.

8.4 Vaccination schedule for patients with IBD

An overview of an adult immunization schedule for patients with IBD is presented in Table 10. Ideally, vaccination history should be obtained at diagnosis and any outstanding vaccinations should be administered. If clinically safe to delay immunosuppressive therapy, any outstanding live vaccinations should be considered prior to starting immunosuppression, as per recommendation 8.1.

Table 10: Adult immunization schedule for patients with IBD

IBD-SPECIFIC VACCINATION PROGRAM	Dosing, schedule, and remarks	Type of vaccine*	At diagnosis	At diagnosis and during follow up	Strongly recommended before immunosuppressive treatment
Inactivated influenza [trivalent/quadrivalent or high dose]	Annual vaccination recommended for all patients on immunosuppressive therapy, according to national guidelines.	Non-live		YES	YES

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Zoster recombinant [RZV] [preferred]	For all patients ≥50 years. Consider in patients <50 years at increased risk of herpes zoster infection.	Non-live			YES
Zoster live [ZVL]	Use only if RZV is unavailable and patient is immunocompetent	Live-attenuated vaccine			YES
Pneumococcal conjugate 13-valent [PCV13] and polysaccharide 23-valent [PPSV23]	Single dose of PCV13 followed by PPSV23 after 8 weeks, and a PPSV23 booster after 5 years. Additional PPSV23 booster according to national guidelines. If PPSV23 provided first, then administer a single dose of PCV13 after 1 year and a PPSV23 booster after 5 years. Additional PPSV23 booster	Non-live	YES	YES	YES

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	according to national guidelines.				
Hepatitis A [Hep A] **	Consider hepatitis A vaccination. Schedule and dosage according to national guidelines.	Non-live		YES	
Human papillomavirus [HPV]	Two or three doses depending on age, for unvaccinated patients, both sexes.	Non-live	YES	YES	
Hepatitis B [Hep B]***	Three-dose series. Additional booster might be necessary according to level of seroprotection. Titres should be regularly checked.	Non-live	YES	YES	YES
ROUTINE VACCINATION PROGRAM	**Dosing, schedule and remarks**	**Type of vaccine**	**At diagnosis**	**At diagnosis and during follow up**	**Strongly recommended before immunosuppressive treatment**
Tetanus, diphtheria, pertussis [Tdap or	If previously immunized, single	Non-live	YES	YES	

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Td]	dose of Tdap, then Td or Tdap every 10 years according to national guidelines.				
Meningococcal vaccines****	For patients at high risk of invasive meningococcal disease. Schedule and dosage according to national guidelines.	Non-live	YES	YES	
Measles, mumps, rubella [MMR]	Adults without evidence of immunity should receive 2 doses separated by at least 28 days.	Live-attenuated vaccine	YES		YES
Varicella	2 doses 4–8 weeks apart only in patients with no history of chickenpox or shingles, no prior immunization, and negative serology for varicella zoster.	Live-attenuated vaccine	YES		YES
Poliomyelitis [inactivated parenteral poliovirus]	Schedule and dosage according to national guidelines.	Non-live	YES	YES	

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SARS-CoV-2	Schedule and dosage according to national guidelines.	Non-live	YES		YES

* Live-attenuated vaccines are generally contraindicated for patients on immunosuppressive therapy

** Indications for hepatitis A vaccination vary by region; in many countries this is only necessary prior to travel to endemic areas

*** ECCO supports the WHO goal to eliminate hepatitis B infection, and the WHO recommends that each region develop their own vaccination goals appropriate to their epidemiological situation in addition to routine vaccination following birth.[534] As such, hepatitis B immunization should be considered in non-immune IBD patients, subject to regional policies.

**** Not routinely used in adult patients with IBD unless a risk factor for invasive meningococcal disease is present; in paediatric patients, vaccines are administered according to national guidelines and routinely used if risk factors are present.

8.5 Vaccination in paediatrics

8.5.1 Risk of infection in newborns
8.5.2 Vaccination of newborns and infants from mothers on immunosuppressive drugs
8.5.3 Vaccination during breastfeeding

See supplementary material.

8.6 Safety screening

8.6.1 Opportunistic infection checklist at IBD diagnosis

Statement 8.2
Before initiation of treatment, preferably at the time of IBD diagnosis, a standardized checklist regarding infection risk and immunization status should be completed [EL5].

Background: See supplementary material.

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8.6.2 Healthcare workers

Statement 8.3

Risk of *M. tuberculosis* infection is increased in healthcare workers with IBD on anti-TNF agents [EL4]. Regular testing for TB is advised for healthcare workers [EL5]. Vaccination programs for routine and specific vaccines should be closely followed [EL5].

Background: See supplementary material.

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9 Disclaimer

The ECCO consensus guidelines are targeted at healthcare professionals only and are based on an international consensus process. Any treatment decisions are a matter for the individual clinician and should not be based exclusively on the content of the ECCO consensus guidelines. ECCO and/or any of its staff members and/or any consensus contributor may not be held liable for any information published in good faith in the ECCO consensus guidelines.

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11 Conflict of interest statement

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

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