A correction notice has been published, see:
https://doi.org/10.1093/ecco-jcc/jjac104

Journal of Crohn's and Colitis, 2021, 879–913
doi:10.1093/ecco-jcc/jjab052
Advance Access publication March 17, 2021
ECCO Guideline/Consensus Paper

ECCO Guideline/Consensus Paper

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,o] C. Abreu,[f] A. Albuquerque,[g] M. Allocca,[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,o] C. Maaser,[q] L. de Ridder,[r] C. Taxonera,[s,o] 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, 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, and 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 -, Rozzano [Mi], Italy, and Humanitas University, Department of Biomedical SciencesMilan, Italy [i]Hospital Universitari Mútua Terrassa, Digestive Diseases Department, Terrassa, Catalonia, and 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, UK [l]Department of Gastroenterology, Venizeleio General Hospital, Heraklion, Greece [m]Department of Gastroenterology, Sheba Medical Center, Ramat Gan, Israel, and 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, and 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, Lüneburg, Germany [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, QC, Canada [v]University Hospital Zürich, Department of Gastroenterology and Hepatology, Zürich, Switzerland [w]Department of Infectious Diseases, Tourcoing Hospital, Tourcoing, France

Corresponding author: Torsten Kucharzik, Department of Gastroenterology, Klinikum Lüneburg, University of Hamburg, Bögelstr. 1, 21339 Lüneburg, Germany. Email: Torsten.Kucharzik@klinikum-lueneburg.de

Key Words: Opportunistic infections; vaccination; inflammatory bowel disease; ECCO guidelines

1. Introduction

The introduction and broad use of new immunosuppressive agents, including biologic agents and JAK inhibitors, have revolutionised 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 recognise, 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 organise this work, 35 PICO [formatted as population, intervention, control, and outcomes] questions were raised by the coordinators, which 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 who 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, 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 randomised 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 body mass index [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 categorised 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] Whereas systemic steroids, thiopurines, and anti-tumour necrosis factor [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, 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 randomised 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-mercaptopurine [MP] and those on combination therapies.[4,17] Infliximab confers a particularly high risk, which appears to be higher compared with 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 with 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 with anti-TNF agents.[24,25]

Table 1 categorises IBD therapeutic agents into the following four degrees of immunosuppression: 1] no immunosuppression; 2] selective immunosuppression; 3] low immunosuppression; and 4] moderate-severe immunosuppression. Categorisation 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-severe immunosuppression', which 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

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 Tacrolimus Anti-TNF Tofacitinib Ustekinumab		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. Immunosuppression of anti-TNF is probably higher compared with ustekinumab and tofacitinib

IBD, inflammatory bowel disease; 6-MP, 6-mercaptopurine; TNF,tumour necrosis factor; AZA, azathioprine.
Simplified degree of immunosuppression [the table helps to decide if live vaccines can be administered safely]:
No:
Selective:
Low:
Moderate-severe:

differentiate between moderate and severe systemic immunosuppression. Whereas 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. Whereas 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 with an RR of 1.10 for doses at <5 mg/day in patients >65 years.[29]

3. Viral Infections

3.1. General aspects

Statement 3.1*

Serological 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 before 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.[30,31]

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 hospitalisation 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 human papilloma virus [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 previous 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 with 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

3.2.1. Hepatitis A virus and vaccination

Statement 3.2

In non-immune patients, vaccination for HAV should be considered before commencement of immunosuppressive treatment [EL5]

An 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 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 with 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]

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%; $p = 0.003$].[55]

Furthermore, Esteve *et al.* noted HBV reactivation in two [n = 3] CD patients on withdrawal of infliximab therapy. No reactivation occurred in the third patient who was on NA prophylaxis.[56]

For decades, long-term prednisone, azathioprine, or both have been known to favour the replication of HBV in patients who are HBsAg positive.[57]

It is recommended that CHB patients should ideally start prophylaxis [tenofovir or entecavir] 2 weeks before the introduction of immunosuppressants, and this should be continued for 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.[53,58]

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 previous HBV infection [HB core Ab-positive, HBsAg-negative] [EL3]

Patients with evidence of previous 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.[51,54,59,60] In patients receiving anti-TNF agents for various conditions, including IBD, Perez-Alvarez *et al.* found a reactivation rate of 5%.[55]

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.[58] Consultation with a hepatologist or infectious disease specialist should be sought in unclear situations.

3.2.3. Hepatitis C

3.2.3.1. Antiviral treatment

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]

Hepatitis C treatment has been revolutionised 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.

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 an SVR after completion of DAA therapy in all patients. SVR after DAA therapy did not seem to be affected by immunosuppressive therapy.[61] 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.[62] 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.[63] The possibility of new-onset colitis after starting treatment with sofosbuvir and simeprevir[64,65] has been reported in two 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.[66] Ribavirin therapy for 3 weeks in patients with severe hepatitis E leads to rapid improvement of liver enzymes and function.[66,67]

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.[68]

HEV genotype 3 causes severe disease, including chronic hepatitis E, in immunosuppressed persons. Chronic infections do not occur in otherwise healthy individuals.[66,67,69]

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.[66,69] There is currently no licensed vaccine for HEV.[67] 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.[70]

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 with 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.[71] 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 seven 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 treatment. Although two patents died, this was not attributable to azathioprine.[72] TNF-α activates viral replication and pathogenesis of HIV-1.[73] In a systematic review on the efficacy and safety of six biologics [rituximab, etanercept, adalimumab, alefacept, infliximab, ustekinumab] for several inflammatory conditions [including three IBD patients] in HIV-infected individuals,[74] there were 37 treatment episodes described and 33 episodes [89%] where anti-TNF agents were used. The efficacy and the infectious and non-infectious complications were comparable to reports from HIV-uninfected patients, but 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 [two 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].[73]

Vedolizumab has shown some benefits in sustained virological control of the simian immunodeficiency virus.[75] In a case report, an HIV-infected man with CD achieved clinical remission with vedolizumab while on ART therapy [1-year follow up].[76] Whereas 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],[76] more data are needed.

In a case series of 13 patients with HIV-associated psoriasis, the four patients who received methotrexate developed leukopenia, with one 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.[77,78]

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.[74]

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.[79,80] Herpes simplex virus [HSV] can cause severe disease in immunocompetent individuals, including keratitis, encephalitis, and retinitis.[79] In a prospective study, IBD patients receiving azathioprine therapy self-reported significantly more skin or genital herpes flares than patients on mesalazine.[81] Reactivation may cause severe localised systemic infections with significant morbidity and mortality, including encephalitis,[82,83] meningitis,[84] pneumonia,[85] oesophagitis,[86] and colitis.[87,88] There is no vaccine available for HSV. Patients should be asked if they have a history of HSV infection before 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.[89]

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.[38] The risk to patients receiving immunosuppressive therapy is further increased. In CD, a retrospective cohort study revealed that corticosteroid use conferred an RR of 1.78 [95% CI: 1.10–2.88]; in UC, steroids and anti-TNF agents conferred an RR of 1.99 [95% CI: 1.64–2.42] and 2.29 [95% CI: 1.52–3.45], respectively.[90]

Before 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].[91] This cohort included a population of 59 individuals on anti-TNF agents who received ZVL, including 12 [20%] who were also taking thiopurines.[92] No cases of disseminated varicella infection were observed within 42 days of vaccination.

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 hazard ratio [HR]: 0.63; 95% CI: 0.30–1.33].[91] Wasan *et al*. observed a blunted immune response in patients with IBD on immunosuppressive therapy.[93] A post-hoc sub-analysis of a large randomised controlled trial [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; $p = 0.70$].[94] However, a second large database study did suggest efficacy in those inadvertently vaccinated while receiving anti-TNF agents; of 551/66 751 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].[95]

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.[96] 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 [$n = 61$].[97] A phase 3 placebo-controlled RCT evaluated the efficacy of RZV in recipients of haemopoietic stem cell transplants.[98] 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].[99]

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].[100] 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,[101] 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 USA.[102] However, only certain countries in the European Union have varicella vaccine programmes. 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.[103] 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.

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.[104]

3.4.3. Cytomegalovirus infection

3.4.3.1. When to test?

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]

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% to 30% in steroid-refractory acute colitis.[105] Concurrent CMV colitis is associated with a major risk of poorer outcomes, including toxic megacolon, colectomy, rescue therapy, and increased rate of disease flares.[106–111] A recent retrospective cohort study of 257 UC patients followed for 10 years revealed that CMV colitis was an independent predictor of hospitalisation and surgery [HR: 2.27; 95% CI: 1.12–4.60].[112] Finally, a meta-analysis revealed that IBD patients with concurrent CMV infection had a poorer prognosis than patients without CMV.[113] 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.[114] 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.[115] Other studies found an association with immunosuppressive therapy and steroid refractoriness.[116,117] 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.[33,118–120] Concurrent CMV infection increased the risk of steroid refractoriness by 2.34-fold in IBD patients compared with patients without CMV.[118] Exposure to thiopurines [OR: 1.56; 95% CI: 1.01–2.39] but not to anti-TNF agents increased the risk of CMV reactivation.[33]

These data support the recommendation to screen for CMV colitis in active IBD patients who are not responding to immunosuppressive therapy.

3.4.3.2. Testing for CMV infection

Statement 3.10*

Immunohistochemistry [IHC], possibly tissue polymerase chain reaction [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

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 antigenaemia assay, and 60.0% [95% CI: 46.5–73.5] for blood PCR [bPCR].[121]

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 antigenaemia 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.[122,123] 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 antigenaemia 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].[124]

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].[121]

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.*[125] 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.[125] Tissue from the base and edges of ulcers were found to have the highest densities of CMV-positive cells.[126]

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 biopsies for CD was proposed by McCurdy *et al.*[127] to achieve an 80% probability of CMV detection.

A recent retrospective study on 25 IBD patients with positive tPCR found that although 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.[128]

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 standardised 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.[121] 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.[129]

3.4.3.3. How to deal with immunosuppressive treatment?

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]

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.[109,115,127] This form of CMV infection is a localised 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.[33]

Based on this indirect information or mechanistic hypothesis, several therapeutic schedules have been proposed, such as rapid steroid tapering[106,130] or administration of infliximab, which is considered to have a lower risk of CMV reactivation than other immunosuppressants such as thiopurines.[33,114] Recently, two case reports proposed vedolizumab for the treatment of steroid-resistant colitis with CMV reactivation,[131,132] 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.[106,109,115,127,128,130,133–140] Moreover, CMV clearance may parallel the achievement of remission induced by immunosuppressants, even in patients who 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.[135] 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.[141] 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.[142] These cases are characterised by a mononucleosis-like syndrome or CMV syndrome [positive

serum PCR with fever, malaise, leukopenia, low platelet count, and elevated liver enzymes].[143]. 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.[144,145] There is limited information on the relationship between the evolution of UC and tissue viral load, as measured by viral inclusions in IHC[146,147] or CMV DNA copies.[125] 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.[143] 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.

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.[148,149] Impairment of T cell function may lead to loss of control over B cell proliferation with a potential risk of B cell lymphoma.[150–155] The vast majority [up to 95%] of the adult population is EBV seropositive due to childhood or adolescent exposure.[156,157] In EBV-IgG negative post-transplant patients treated with immunosuppressive therapy, primary EBV infection increases the risk of post-transplant lymphoproliferative disease.[158,159] 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][148,160]; in the CESAME cohort data, over 40% of the patients who developed lymphoma had EBV-positive tumours.[36] Afif *et al*. reported that 75% of lymphomas in IBD patients were EBV-positive.[35] Multiple case reports or small case series of lymphoma following a primary EBV infection in immunosuppressed IBD patients have been published.[161–165]

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.[166,167]

Despite this concern, there are no comparative or prospective data to support the benefit of routine assessment of EBV serology. Nonetheless, screening for previous 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.[163,168–172] Discontinuation of immunosuppression is the primary therapeutic intervention and results in resolution in a high proportion of patients.[169]

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 hospitalisation. Steroids were the only medications independently associated with influenza risk.[173] Whereas the incidence of influenza was not greater in IBD patients receiving immunosuppressive therapy[174] during the 2009 H1N1 pandemic, immunosuppression is generally considered to enhance the risk of severe or complicated influenza infection.[175] A retrospective study performed in 12 European IBD centres during the H1N1 pandemic identified 25 patients who developed influenza, of whom 88% were immunosuppressed, 28% were hospitalised, and 12% were admitted to the intensive care unit.[176]

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.[177] Annual vaccination in accordance with national guidelines is recommended, particularly in the post COVID-19 era. Compliance with recommendations remains poor,[178,179] but uptake of influenza vaccination in CD patients increased between 2005 and 2012.[180] Vaccination education programmes, patient information leaflets, and specialised infectious disease consultations have proven effective in improving uptake of influenza vaccines.[181–183]

There are 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.[184–187] The use of anti-TNF agent monotherapy may also reduce response to vaccination.[187–190] The timing of vaccination relative to infliximab infusion does not affect the achievement of serological protection.[190] The persistence of seroprotection is also lower in patients on anti-TNF agents.[191] The immune response nevertheless remains sufficient to warrant annual vaccination. Baricitinib has limited impact on vaccine response in patients with RA, but data are lacking in IBD patients.[192,193] In a small study, patients receiving vedolizumab had similar vaccine responses as healthy controls.[194] Data on influenza vaccine efficacy and use of ustekinumab are lacking.

Various strategies have been developed to optimise influenza vaccination in IBD patients. Temporary methotrexate discontinuation for 2 weeks after vaccination improves immunogenicity in RA patients.[195] Patients on anti-TNF agent monotherapy who received a high-dose influenza vaccine had significantly higher post-immunisation antibody levels compared with standard dose,[194] whereas a booster immunisation was ineffective in two independent trials.[196,197] Last, influenza vaccination appears safe in patients with IBD and is not associated with a risk of flare.[191,198]

3.6. Immunosuppressive treatment during viral infections

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]

The severity of reported cases of primary varicella[199] and HSV infection[200–202] 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.[21,100] In severe cases, defined as multi-dermatomal involvement [two non-adjacent dermatomes, three to six adjacent], disseminated [more than seven dermatomes], or ophthalmic,[100] 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.[18,203]

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 hospitalisation.[173] 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 rash or fever but may include life-threatening giant-cell pneumonitis or sub-acute measles encephalopathy.[204,205] 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.[206] 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.

3.7. Antiviral treatment in immunosuppressed IBD patients

Statement 3.15*

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

Immunocompromised patients with IBD have an increased risk of influenza compared with individuals without IBD.[173] 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.[81,173,207] 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.[81,208] 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.[209–214]

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 h of rash onset and should 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.[215–219]

3.8. Human papilloma virus

3.8.1. HPV, cervical cancer, and immunosuppression

Statement 3.16*

Immunosuppressed female IBD patients should undergo annual cervical cancer screening [EL3]

Several studies have shown that immunosuppressive treatment may increase the risk of persistent HPV infection and ultimately cervical cancer. There are 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.[220] 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].[208]

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 with the general population.[37] Similarly, in a recent prospective study, Li *et al*. observed that all patients who developed cervical neoplasia were receiving immunosuppressants.[220]

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.[221] Similarly, Dugué *et al*. demonstrated that azathioprine exposure was associated with an 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.[222] 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.[208] 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.[223] Currently, there are no data on vedolizumab and the occurrence of cervical dysplasia.[224]

3.8.2. Vaccination

Statement 3.17*

Routine prophylactic HPV vaccination is recommended for both young female and young 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 nona-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 nona-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.[225–227] 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.[228] 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].[228] 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.[228] Few studies have evaluated the immunogenicity or safety of quadrivalent and bivalent vaccines in immunocompromised populations.[229–234] One study was conducted in young females with IBD and showed good immunogenic response without significant vaccine-associated side effects.[229]

3.9. Human polyoma virus-2

Serological screening for human polyoma virus-2 [John Cunningham: 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 experience in PML and HIV concluded that the most probable cause of PML was the presence of HIV in combination with immunosuppression.[235]

3.10. SARS-CoV-2

Statement 3.18

During the SARS-CoV-2 pandemic, management of IBD should follow usual standards of care [EL5]

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 identified neither IBD nor immunosuppressive therapy to be risk factors for disease onset.[236–238] 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.[239] 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.[240]

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.[241] 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. Optimising IBD care amidst these limitations is discussed in the ECCO-COVID Taskforce paper.[242]

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.[239] The exceptions are previous corticosteroids, thiopurines, combination therapy with anti-TNF agents and thiopurines, and possibly 5-ASA. Although 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 under way. 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, when undergoing routine testing before a scheduled infusion. At the other extreme, there have been cases of acute severe colitis in those with concurrent COVID-19 infection.[243] For the latter scenario, a Research and Development [RAND] panel-based guidance has been developed.[244] 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,[245,246] with three phase 3 trials having released significant results.[247–249] The UK launched the first national vaccination programme on 8 December 2020,[250] entailing the two-dose mRNA vaccine BNT162b2, a vaccine with response rates of 95% [$p < 0.0001$][247] and a favourable safety profile. The Oxford/Astra-Zeneca COVID-19 vaccine 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 in any patients undergoing treatment with immunosuppressive therapy. With mRNA vaccination itself being a novel immunisation 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[251] and the British Society of Gastroenterology [BSG].[252] 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 biologics 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 affected by immunosuppressive therapy, diagnosing latent tuberculosis infection [LTBI] before starting any treatment is advisable.[253–255] Furthermore, exposure to biologic 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].[256]

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 Systematic Review.[257]

According to a systematic review in both rheumatological and non-rheumatological diseases,[258] 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.

There are a few reports of TB reactivation among patients treated with vedolizumab,[22,259] but 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.[260] Indirect comparisons between ustekinumab and anti-TNF agents concluded that the incidence rate of TB was lower among ustekinumab-treated patients than among those treated with anti-TNF agents [incidence rate: 0.02; 95% CI: 0.00–0.06 vs 0.28; 95% CI: 0.21–0.37 per 100 patient-years, respectively].[261] 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.[262]

In patients treated with methotrexate or azathioprine, a short course of corticosteroids, or ciclosporin, several studies showed that the risk of TB is not higher when compared with placebo alone, and thus no treatment of LTBI is recommended in these patients.[258,263,264] Due to TB cases diagnosed in patients treated with anti-TNF agents despite a negative TB screening preceding anti-TNF therapy,[265,266] annual re-screening could be considered,[267] especially for patients with a higher TB risk [living or travelling in an 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.[268] 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 tuberculin skin test [TST] or interferon-gamma release assay [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 before initiating any biologic 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 patients.[269] Therefore, it is recommended to perform early screening for LTBI at the time of IBD diagnosis,[270] 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[271–273];
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.[274]

Individuals vaccinated with Bacillus Calmette-Guerin [BCG] may react positively to purified protein derivate, resulting in a positive TST.[275,276] 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.[277] However, repeated BCG vaccination or exposure to non-tuberculous mycobacteria can result in positive TST results.[278] 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 rheumatological or IBD patients.[269,277,279–282] 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,[267] 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.[283]

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.[284]

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*.[285] 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%,[286] although IGRA sensitivity seems significantly influenced by immunosuppression, similar to TST.[287–289]

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.[290,291] 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.[292,293] 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.[294,295]

In case both TST and IGRA are performed, due to limited data on better performance of combining both in non-vaccinated BCG persons,[296] IGRA determination should precede or be concomitant with TST, as TST may increase the production of interferon-γ in IGRA tests.[297]

4.2. Chemoprophylaxis

Statement 4.3

Patients diagnosed with LTBI before biologic 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, biologic 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].[271,298–300] Randomised trials have shown that INH provides approximately 90% protection against TB after completion of a 9-month course, and 60–80% protection after a 6-month course.[301] However, the regimen is associated with poor adherence and toxicity. More recently, two open-label, randomised, 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.[302] The other trial compared a 4-month regimen of rifampicin. Both trials revealed better adherence when compared with the standard regimen.[303] 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.[304] 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.[280,298,305–307]

No prospective or controlled data are available on the ideal timing of starting biologic or small-molecule therapy once TB treatment has begun. In case of active TB, biologic 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.[309] 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 risks. Importantly, positive TST or IGRA may remain positive after successful TB therapy[310]; 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.[311] One of the most prevalent infections in immunosuppressed patients with IBD is bacterial pneumonia.[19,312] The 1-year mortality is lower in patients with IBD vaccinated against pneumococcus [2.1%] compared with those not vaccinated [4.5%].[313]

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	[271,298–301,308]
Rifapentine +INH	Rifapentine 900 mg plus INH 900 mg once weekly; 12 doses	3	Not inferior to INH 9 months	Better adherence	[302]
Rifampicin	600 mg/day; maximum [10 mg/Kg]	4	Not inferior to INH 9 months	Better safety and adherence	[303]

INH, isoniazid.

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.[314] The same was observed in two independent cohorts for PPSV23.[315,316] 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.[317] One study showed that PCV13 was more immunogenic than PPSV23 after 4 weeks.[318] Overall, the administration of PCV13 was highly immunogenic. However, a slightly lower seroprotection rate was observed in those using anti-TNF agents.[319]

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.[320] 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%to 75%. Real-time PCR on urine and serum is not more sensitive than culture.[321] Serological testing is also available; a 4-fold increase in titre between the acute and convalescent titre is required for a definitive serological 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.

Immunosuppressive therapy is considered to confer a high risk for infection with *L. pneumophila*.[322] 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.[323] Invasive *L. pneumophila* infections, some with fatal outcome, have been reported in patients on immunomodulators for IBD or rheumatological conditions.[324,325] 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, and a few other cases have been reported during the development programmes of vedolizumab and tofacitinib.[326]

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.[327–337] 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,[338] aortitis,[339] or septic arthritis,[340,341] 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.[342–345]

Immunosuppressive therapy is considered to confer a high risk for *L. monocytogenes* infection, which causes primarily severe septicaemia and meningitis accompanied with considerable mortality.[346] Compared with other immunosuppressants, anti-TNF agents appear to confer a particular risk for serious infection.[327,347–361] 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/sulphamethoxazole [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].

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.[353] 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 re-institution of immunosuppression after treatment of active infection.[347]

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 hospitalisation. A meta-analysis including 12 studies reported a significant association between community-acquired CDI and IBD [OR 3.72],[362] which was also observed in paediatric patients.[363] 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.[364] Patients with colonic involvement seem more likely to develop CDI [OR 2.76],[365] although the risk of CDI infection [7%] is not negligible in IBD patients without colon involvement.[366] 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; $p = 0.001$].[367]

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.[365] 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,[364] which was confirmed in an independent cohort.[367] 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 on short- and long-term IBD-related outcomes, including colectomy and mortality rates. CDI also results in longer hospitalisations, escalation in IBD therapy, increased readmission rates, and increased in-hospital expenditures in adult[368,369] and paediatric[363,370] 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.[365] A later study confirmed that CDI increased mortality among patients with IBD [HR 2.28].[364] 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.[371] 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 h 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 neutralisation assay [CCNA]. Recently, ultrasensitive toxin immunoassays have been developed that are up to three orders of magnitude more sensitive than EIAs.[372] 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.[373] 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.[371,374] 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 optimise CDI diagnosis.[375] 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.[375] 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.[375]

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.[376,377] Moreover, EIAs designed to detect only toxin A are likely to under-report 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.[373,375,376] 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.[378,379] Given its high sensitivity and the potential for false-positive results, the NAAT test has been suggested in algorithms together with EIAs.[373,375] CCNA for *C. difficile* toxin B still represents the diagnostic gold standard.[380] Toxigenic culture, based on detection of toxin production after isolation in culture, has increased sensitivity over CCNA and can be used as an alternative.[381] However, these reference methods are not considered practical, due to the lengthy turnaround time [24–48 h] and requirements for special laboratory experience. Interestingly, a recent retrospective study suggested that toxin+ IBD patients compared with toxin- PCR+ IBD patients had a significantly higher response rate to antibiotics and lower chances of requiring IBD therapy escalation.[382]

Endoscopy is not recommended as a diagnostic tool for CDI as pseudomembranes are rarely found and their absence does not exclude infection.[383] Pseudomembranes were only reported in 13% of hospitalised IBD patients with CDI, a finding that was independent of immunosuppressant use.[384]

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[385,386] [Table 3]. Fidaxomicin, a narrow-spectrum antibiotic introduced in 2011, is non-inferior to vancomycin for clinical response to a first episode of CDI.[387,388] 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.[389]

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 create diagnostic challenges when assessing for CDI treatment failure. In this setting, repeated testing in patients with ongoing 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.[389] 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.[390] Other antibiotics, such as rifaximin, may be considered in case of recurrent disease.[389] Faecal microbiota transplantation [FMT] is recommended in case of multiple recurrences of CDI.[389,391] Prevention of CDI recurrence following FMT ranges from 70% to 90% in both observational and randomised clinical trials in patients without IBD,[392] with similar rates in patients with IBD.[393] Use of FMT has also been reported in some specific settings, such as patients with CDI and ileal pouch anal anastomosis.[394] Further studies are required to determine the optimal regimen and indication for 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.[395] Bezlotoxumab, a monoclonal antibody against *C. difficile* toxin B, reduced rates of recurrent CDI compared with placebo in non-IBD patients receiving antibiotic treatment for CDI.[396]

Thiopurines and anti-TNF agents have been variously associated with an increased risk of CDI in observational studies,[367,397] 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 no cases in patients exposed to placebo. Further studies are required

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 shock, ileus, megacolon]	VAN, 500 mg 4 times daily [by mouth, nasogastric tube, or rectal] PLUS intravenous metronidazole [500 mg every 8 h]	If ileus: consider adding rectal instillation of VAN [retention enema: 500 mg in 100 ml, 4 times daily]
First recurrence	VAN 125 mg orally 4 times daily for 10 days	If metronidazole was used for the initial episode
	OR	If VAN was used for the initial episode
	prolonged tapered and pulsed VAN regimen [eg, 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]	If VAN was used for the initial episode
	OR FDX 200 mg twice daily for 10 days	
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 Infectious Diseases Society of America [IDSA] and Society for healthcare Epidemiology of America [SHEA].[389]

VAN, vancomycin; FDX, fidaxomicin.

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.

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 an ubiquitous agent, the risk in IBD patients is low [EL5]

Background: see Supplementary material, available as Supplementary data at *ECCO-JCC* online.

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.[398] Different vaccines against different serogroups are available [Men-C, Men-C-ACYW, and Men-B], and country-specific immunisation guides have been adopted based on local epidemiology.[399–401]

Meningococcal vaccination is recommended in persons at a higher risk for invasive meningococcal disease due to underlying medical conditions [eg, anatomical 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 [eg, travellers to countries with hyperendemic or epidemic meningococcal disease, microbiologists routinely exposed to *Neisseria meningitidis* isolates, military recruits, and college students in residential housing.[399,400]

IBD may be associated with hyposplenism, which has been shown to be more frequent in UC than in CD.[402–406] Hyposplenism may be associated with colonic IBD, transient and related to the severity and extension of colitis.[404,405] 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.[407,408] The first case was meningococcal meningo-encephalitis in a 51 year-old female with CD treated with certolizumab pegol for 6 months [dosage and concomitant immunosuppression unspecified].[407] 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 of 40 mg per week.[408] 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 hospitalisation 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 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.[409] 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 cohorts, 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.[409]

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 authors' 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, available as Supplementary data at *ECCO-JCC* online.

6.1. *Pneumocystis jirovecii* infection

Statement 6.3

For patients with IBD on triple immunosuppressive therapy [including steroids, methotrexate, thiopurines, biologics], 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]

Background: see Supplementary material, available as Supplementary data at *ECCO-JCC* online.

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 7.1*

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]

Background: see Supplementary material, available as Supplementary data at *ECCO-JCC* online.

7.2. Infectious diarrhoea in immunosuppressed IBD patients

Background: see Supplementary material, available as Supplementary data at *ECCO-JCC* online.

7.3. Malaria

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, available as Supplementary data at *ECCO-JCC* online.

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, available as Supplementary data at *ECCO-JCC* online.

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.[410–412] The immunisation status of IBD patients should be markedly improved. In this guideline, an overview of a routine vaccination programme and an IBD-specific programme that is relevant for each patient will be presented [Table 5]. Specific vaccination in patients with IBD is discussed in the different sections in this guideline which address specific viral and bacterial pathogens. As immunisation programmes 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 Furer *et al.*[413]].

- The individualised vaccination programme should be explained to the patient by the IBD specialist, thus providing a basis for shared decision making. The programme 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 immunisation may be impaired by immunosuppression [eg, 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.

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 are 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,[414] UK Green Book [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/655225/Greenbook_chapter_6.pdf] [accessed November 7, 2020] and the European League Against Rheumatism [EULAR][413] suggest that live vaccination may be safe during low-dose immunosuppression [see Table 1 for definition]. This chapter summarises 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,[91,93] and even anti-TNF agents.[92,415,416] These patients will have had some pre-existing immunity from previous 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[417] [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,[418,419] with some cases demonstrating adequate immunoprotection.[418–420] A recent prospective, multicentre, controlled, observational, Swiss study revealed that 15 immunosuppressed travelers, given yellow fever vaccine while on low-dose methotrexate [20 mg/week or less], responded serologically with no serious reactions.[421]

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.[422]

Documentation of vaccination with two doses of the live attenuated measles vaccine is recommended as an adequate measure to verify immunity.[423] Vaccinated immunocompromised IBD patients have similar antibody titres as the general population.[424] Documented immunisation supersedes serological 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.[423] Serological 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.

Table 4. Suggested time frame between stopping immunosuppressants and live vaccination, considering drug elimination half-life.[2,218,429–432]

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 h	1 month	1 month
Thiopurines[a] [azathioprine and 6-MP[b]: approximately 2 h]	Several days [6-TGN[c]]	3 months	1 month
Methotrexate, low dose [adults]	3–10 h	1 month	1 month
Tofacitinib	3 h	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[d,e]	8.4 h [10–27]	1 month	1 month
Tacrolimus[e]	23–46 h	1 month	1 month
Vedolizumab[f]	25 days	3–4 months	1 month
Ustekinumab	Approximately 19 days	3 months	1 month

[a]Zoster live vaccine [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].

[b]6-MP: 6-mercaptopurine.

[c]6-TGN: 6-thioguanine nucleotides.

[d]Ciclosporin modified.

[e]Immediate-release formulations

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

Table 5. Adult immunisation schedule for patients with IBD.

	Dosing, schedule, and remarks	Type of vaccine[a]	At diagnosis	At diagnosis and during follow-up	Strongly recommended before immunosuppressive treatment
IBD-specific vaccination programme					
Inactivated influenza [trivalent/quadrivalent or high dose]	Annual vaccination recommended for all patients on immunosuppressive therapy, according to national guidelines	Non-live		Yes	Yes
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 according to national guidelines	Non-live	Yes	Yes	Yes
Hepatitis A [Hep A][b]	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][c]	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 programme					
Tetanus, diphtheria, pertussis [Tdap or Td]	If previously immunised, single dose of Tdap, then Td or Tdap every 10 years according to national guidelines	Non-live	Yes	Yes	
Meningococcal vaccines[d]	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	Two doses 4–8 weeks apart only in patients with no history of chickenpox or shingles, no previous immunisation, 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	
SARS-CoV-2	Schedule and dosage according to national guidelines	Non-live	Yes		Yes

IBD, inflammatory bowel disease.

[a]Live-attenuated vaccines are generally contraindicated for patients on immunosuppressive therapy.

[b]Indications for hepatitis A vaccination vary by region; in many countries this is only necessary before travel to endemic areas.

[c]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.[205] As such, hepatitis B immunisation should be considered in non-immune IBD patients, subject to regional policies.

[d]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.

8.3. Scheduling live vaccination in IBD

Ideally, live vaccines should be administered before 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 4].

A systematic review of 64 studies of vaccination in immunosuppressed populations demonstrated that adverse events following live vaccination are relatively rare.[425] 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.

Immunisation of close -contacts ['cocoon strategy'] is an important means of protecting immunosuppressed patients.[426] 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 minimised by simple precautions [Green Book, Chapter 6].[427] 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. Although rarely used, vaccination of close contacts with live smallpox and oral polio vaccines would pose a significant risk for immunosuppressed IBD patients.[414,428]

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 methotrexate and 6 months for other immunosuppressants [eg, chemotherapy, anti-rejection drugs; Green Book, Chapter 6].[427]

Whereas 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.[429] Both drug elimination and immune reconstitution influence safety. A rule of thumb is to use five times the elimination half-life of a drug, as there are no significant concentrations of a medication after this period.[429] This is a strategy also used by other guidelines addressing this issue.[429] 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 4 presents the minimal intervals between stopping immunosuppressive therapy and the administration of live vaccines.

8.4. Vaccination schedule for patients with IBD

An overview of an adult immunisation schedule for patients with IBD is presented in Table 5. 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 before starting immunosuppression, as per recommendation 8.1.

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, available as Supplementary data at *ECCO-JCC* online.

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 standardised checklist regarding infection risk and immunisation status should be completed [EL5]

Background: see Supplementary material, available as Supplementary data at *ECCO-JCC* online.

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 programmes for routine and specific vaccines should be closely followed [EL5]

Background: see Supplementary material, available as Supplementary data at *ECCO-JCC* online.

Funding

This project was initiated, funded, and supported by ECCO.

Conflict of Interest

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.

Disclaimer

The ECCO consensus guidelines are targeted at health care 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.

Acknowledgement

We would like to acknowledge the ECCO National Representatives, who acted as external reviewers and provided suggestions on the statements: Christoph Högenauer [Austria], Triana Lobaton [Belgium], Željko Krznarić [Croatia], Dana Duricová [Czech Republic], Signe Wildt [Denmark], Karin Kull [Estonia], Clas-Göran af Björkesten [Finland], Tuire Ilus [Finland], Stephanie Viennot [France], Dominik Bettenworth [Germany], Giorgos Bamias [Greece], Dimitrios Christodoulou [Greece], Matti Waterman

[Israel], Henit Yanai [Israel], Aleksejs Derovs [Latvia], Svetlana Turcan [Moldova], Rosa Isadora [Portugal], Ana Isabel Vieira [Portugal], Mihai Mircea Diculescu [Romania], Adrian Goldiș [Romania], Alexander Potapov [Russia], Mirjana Cvetkovic [Serbia], Srdjan Djuranovic [Serbia], Manuel Barreiro de Acosta [Spain], Ana Gutierrez [Spain], Filiz Akyüz [Turkey]. The following external experts also reviewed and provided suggestions on the statements: Pradeep Kakkadasam Ramaswamy [Australia], Gulustan Babayeva-Sadigova [Azerbaijan], Annick Moens [Belgium], Lieven Pouillon [Belgium], Oliver Bachmann [Germany], Christina Kapizioni [Greece], Konstantinos Katsanos [Greece], Spyros Siakavellas [Greece], Vineet Ahuja [India], Ciaran Judge [Ireland], Rachele Ciccocioppo [Italy], Federica Furfaro [Italy], Loris Lopetuso [Italy], Giuseppe Ribaldone [Italy], Simone Saibeni [Italy], Ignacio Catalán-Serra [Norway], Joana Roseira [Portugal], Anna Kagramanova [Russian Federation], Yago González Lama [Spain], Robin Dart [UK], Klaartje Bel Kok [UK], Nuru Noor [UK]. References 433–533 are available in Supplementary material.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Rahier JF, Ben-Horin S, Chowers Y, *et al.*; European Crohn's and Colitis Organisation [ECCO]. European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009;**3**:47–91.
2. Rahier JF, Magro F, Abreu C, *et al.*; European Crohn's and Colitis Organisation [ECCO]. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014;**8**:443–68.
3. Dave M, Purohit T, Razonable R, Loftus EV Jr. Opportunistic infections due to inflammatory bowel disease therapy. *Inflamm Bowel Dis* 2014;**20**:196–212.
4. Toruner M, Loftus EV Jr, Harmsen WS, *et al*. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008;**134**:929–36.
5. Ainley C, Cason J, Slavin BM, Wolstencroft RA, Thompson RP. The influence of zinc status and malnutrition on immunological function in Crohn's disease. *Gastroenterology* 1991;**100**:1616–25.
6. Park MA, Li JT, Hagan JB, Maddox DE, Abraham RS. Common variable immunodeficiency: a new look at an old disease. *Lancet* 2008;**372**:489–502.
7. Hammer SM. Clinical practice. Management of newly diagnosed HIV infection. *N Engl J Med* 2005;**353**:1702–10.
8. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:2294–300.
9. Lichtenstein GR, Feagan BG, Cohen RD, *et al*. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol* 2012;**107**:1409–22.
10. Cottone M, Kohn A, Daperno M, *et al*. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011;**9**:30–5.
11. Naganuma M, Kunisaki R, Yoshimura N, Takeuchi Y, Watanabe M. A prospective analysis of the incidence of and risk factors for opportunistic infections in patients with inflammatory bowel disease. *J Gastroenterol* 2013;**48**:595–600.
12. Osterman MT, Sandborn WJ, Colombel JF, *et al*. Crohn's disease activity and concomitant immunosuppressants affect the risk of serious and opportunistic infections in patients treated with adalimumab. *Am J Gastroenterol* 2016;**111**:1806–15.
13. Ananthakrishnan AN, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. *J Crohns Colitis* 2013;**7**:107–12.
14. Tosca J, Garcia N, Pascual I, *et al*. Clinical assessment of risk factors for infection in inflammatory bowel disease patients. *Int J Colorectal Dis* 2020;**35**:491–500.
15. Wheat CL, Ko CW, Clark-Snustad K, Grembowski D, Thornton TA, Devine B. Inflammatory Bowel Disease [IBD] pharmacotherapy and the risk of serious infection: a systematic review and network meta-analysis. *BMC Gastroenterol* 2017;**17**:52.
16. Colombel JF, Sandborn WJ, Reinisch W, *et al.*; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383–95.
17. D'Haens G, Reinisch W, Colombel JF, *et al.*; ENCORE investigators. Five-year safety data from ENCORE, a European Observational Safety Registry for adults with Crohn's disease treated with infliximab [Remicade®] or conventional therapy. *J Crohns Colitis* 2017;**11**:680–9.
18. Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology* 2018;**155**:337–46.e10.
19. Colombel JF, Loftus EV Jr, Tremaine WJ, *et al*. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004;**126**:19–31.
20. Singh S, Murad MH, Fumery M, *et al*. Comparative risk of serious infections with biologic and/or immunosuppressive therapy in patients with inflammatory bowel diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2020;**18**:69–81.e3.
21. Zabana Y, Rodríguez L, Lobatón T, *et al*. Relevant infections in inflammatory bowel disease, and their relationship with immunosuppressive therapy and their effects on disease mortality. *J Crohns Colitis* 2019;**13**:828–37.
22. Colombel JF, Sands BE, Rutgeerts P, *et al*. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut* 2017;**66**:839–51.
23. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;**46**:3–15.
24. Pawar A, RJGautam N, Kim SC. Risk of admission to hospital for serious infection after initiating tofacitinib versus biologic DMARDs in patients with rheumatoid arthritis: a multidatabase cohort study. *Lancet Rheumatol* 2020;**2**:PE84–98.
25. Li X, Andersen KM, Chang HY, Curtis JR, Alexander GC. Comparative risk of serious infections among real-world users of biologics for psoriasis or psoriatic arthritis. *Ann Rheum Dis* 2020;**79**:285–91.
26. Bühler S, Eperon G, Ribi C, *et al*. Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases. *Swiss Med Wkly* 2015;**145**:w14159.
27. Miehlke S, Madisch A, Bethke B, *et al*. Oral budesonide for maintenance treatment of collagenous colitis: a randomised, double-blind, placebo-controlled trial. *Gastroenterology* 2008;**135**:1510–6.
28. Münch A, Bohr J, Miehlke S, *et al.*; BUC-63 investigators. Low-dose budesonide for maintenance of clinical remission in collagenous colitis: a randomised, placebo-controlled, 12-month trial. *Gut* 2016;**65**:47–56.
29. Dixon WG, Kezouh A, Bernatsky S, Suissa S. The influence of systemic glucocorticoid therapy upon the risk of non-serious infection in older patients with rheumatoid arthritis: a nested case-control study. *Ann Rheum Dis* 2011;**70**:956–60.
30. Huang ML, Xu X, Shen J, *et al*. Prevalence and factors related to hepatitis B and C infection in inflammatory bowel disease patients in China: a retrospective study. *J Crohns Colitis* 2014;**8**:282–7.
31. Harsh P, Gupta V, Kedia S, *et al*. Prevalence of hepatitis B, hepatitis C and human immunodeficiency viral infections in patients with inflammatory bowel disease in north India. *Intest Res* 2017;**15**:97–102.
32. Hollinger FB, Ticehurst J. Hepatitis A virus. In: *Fields Virology*. 3rd edn. Philadelphia, PA: Lippincott-Raven; 1996:735–82.
33. Shukla T, Singh S, Tandon P, McCurdy JD. Corticosteroids and thiopurines but not tumor necrosis factor antagonists are associated with cytomegalovirus reactivation in inflammatory bowel disease. A systematic review and meta-analysis. *J Clin Gastroenterol* 2017;**51**:394–401.
34. Cohen S, Martinez-Vinson C, Aloi M, *et al*. CMV infection in pediatric severe ulcerative colitis – a multicenter study from the Pediatric Porto Group of ESPGHAN. *Pediatr Infect Dis J* 2017. doi: 10.1097/INF.0000000000001724.
35. Afif W, Sandborn WJ, Faubion WA, *et al*. Risk factors for lymphoma in patients with inflammatory bowel disease: a case-control study. *Inflamm Bowel Dis* 2013;**19**:1384–9.

36. Beaugerie L, Brousse N, Bouvier AM, *et al*.; CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;**374**:1617–25.
37. Allegretti JR, Barnes EL, Cameron A. Are patients with inflammatory bowel disease on chronic immunosuppressive therapy at increased risk of cervical high-grade dysplasia/cancer? A meta-analysis. *Inflamm Bowel Dis* 2015;**21**:1089–97.
38. Ning L, Liu R, Li S, *et al*. Increased risk of herpes zoster infection in patients with inflammatory bowel disease: a meta-analysis of cohort studies. *Eur J Clin Microbiol Infect Dis* 2020;**39**:219–27.
39. Sandborn WJ, Panés J, D'Haens GR, *et al*. Safety of tofacitinib for treatment of ulcerative colitis, based on 4.4 years of data from global clinical trials. *Clin Gastroenterol Hepatol* 2019;**17**:1541–50.
40. Olivera P, Lasa J, Bonovas S, *et al*. Safety of Janus kinase inhibitors in patients with inflammatory bowel diseases or other immune-mediated diseases: a systematic review and meta-analysis. *Gastroenterology* 2020. doi: 10.1053/j.gastro.2020.01.001.
41. Van Damme P, Van Herck K. A review of the long-term protection after hepatitis A and B vaccination. *Travel Med Infect Dis* 2007;**5**:79–84.
42. Park SH, Yang S, Park SK, *et al*. Efficacy of hepatitis A vaccination and factors impacting on seroconversion in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2014;**20**:69–74.
43. Abreu C, Sarmento A, Magro F. Screening, prophylaxis and counselling before the start of biological therapies: a practical approach focused on IBD patients. *Dig Liver Dis* 2017;**49**:1289–97.
44. Zullow S, Farraye FA. Updates on vaccinating the inflammatory bowel disease patient. *Expert Rev Gastroenterol Hepatol* 2019;**13**:229–39.
45. Nelson NP, Link-Gelles R, Hofmeister MG, *et al*. Update: recommendations of the advisory committee on immunization practices for use of hepatitis A vaccine for postexposure prophylaxis and for preexposure prophylaxis for International Travel. *MMWR Morb Mortal Wkly Rep* 2018;**67**:1216–20.
46. Loras C, Gisbert JP, Mínguez M, *et al*.; REPENTINA study; GETECCU [Grupo Español de Enfermedades de Crohn y Colitis Ulcerosa] Group. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. *Gut* 2010;**59**:1340–6.
47. Park SH, Yang SK, Lim YS, *et al*. Clinical courses of chronic hepatitis B virus infection and inflammatory bowel disease in patients with both diseases. *Inflamm Bowel Dis* 2012;**18**:2004–10.
48. Watts A, Bennett WE, Molleston JP, *et al*. Incidence of low seroimmunity to hepatitis B virus in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2017;**65**:551–4.
49. Nguyen HT, Minar P, Jackson K, Fulkerson PC. Vaccinations in immunosuppressive-dependent pediatric inflammatory bowel disease. *World J Gastroenterol* 2017;**23**:7644–52.
50. Jiang HY, Wang SY, Deng M, *et al*. Immune response to hepatitis B vaccination among people with inflammatory bowel diseases: a systematic review and meta-analysis. *Vaccine* 2017;**35**:2633–41.
51. Loras C, Gisbert JP, Saro MC, *et al*.; REPENTINA study, GETECCU group [Grupo Español de trabajo de Enfermedades de Crohn y Colitis Ulcerosa]. Impact of surveillance of hepatitis B and hepatitis C in patients with inflammatory bowel disease under anti-TNF therapies: multicentre prospective observational study [REPENTINA 3]. *J Crohns Colitis* 2014;**8**:1529–38.
52. Pratt P, Nunes D, Long MT, Farraye FA. Improved antibody response to three additional hepatitis B vaccine doses following primary vaccination failure in patients with inflammatory bowel disease. *Dig Dis Sci* 2019;**64**:2031–8.
53. Di Bisceglie AM, Lok A, Martin P, *et al*. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immunesuppressing and anticancer drugs: just the tip of the iceberg? *Hepatology* 2015;**61**:703–11.
54. Morisco F, C F, Rispo A, *et al*. Incidence of Hepatitis B virus reactivation and hepatotoxicity in patients receiving long-term treatment with tumor necrosis factor antagonists. *Clin Gastroenterol Hepatol* 2018;**16**:1964–73.e1.
55. Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, *et al*.; BIOGEAS Study Group. Hepatitis B virus [HBV] reactivation in patients receiving tumor necrosis factor [TNF]-targeted therapy: analysis of 257 cases. *Medicine* 2011;**90**:359–71.
56. Esteve M, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004;**53**:1363–5.
57. Sagnelli E, Manzillo G, Maio G, *et al*. Serum levels of hepatitis B surface and core antigens during immunosuppressive treatment of HBsAg-positive chronic active hepatitis. *Lancet* 1980;**2**:395–7.
58. Lampertico P, Agarwal K, Berg T, *et al*. EASL 2017, Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017;**67**:370–98.
59. Shah R, Ho CY, Kramer JR, et al. Hepatitis B virus screening and reactivation in a national VA cohort of patients with inflammatory bowel disease treated with tumor necrosis factor antagonists. *Dig Dis Sci* 2018;**63**:1551–7.
60. Pereira R, Raposo I, Nery F, Torres T, Risk of hepatitis B virus reactivation in patients treated with anti-TNF agents for immune-mediated inflammatory diseases. *Actas Dermosifiliogr* 2018;**109**:285–7.
61. Hahn KJ, Kohli A, Sims Z, Kottilil S. Durable sustained virologic response after oral directly acting antiviral therapy despite immunosuppressive treatment. *Open Forum Infect Dis* 2015;**2**:ofv091.
62. Ohta Y, Kanda T, Katsuno T, *et al*. Successful sofosbuvir treatment with ribavirin dose reduction for chronic hepatitis C virus genotype 2 infection in a patient with ulcerative colitis: a case report. *BMC Gastroenterol* 2016;**16**:66.
63. von Felden J, Scheurich C, Yamamura J, *et al*. Successful treatment of chronic hepatitis C with ground ledipasvir/sofosbuvir in a patient with Crohn's disease and short bowel syndrome. *J Viral Hepat* 2018;**25**:214–5.
64. Izzo I, Zanotti P, Chirico C, *et al*. Colitis during new direct-acting antiviral agents [DAAs] therapy with sofosbuvir, simeprevir and ribavirin for genotype 1b hepatitis C. *Infection* 2016;**44**:811–2.
65. Sarkar S, Mitchell KA, Lim JK, Oikonomou I, Jakab S. Colitis following initiation of sofosbuvir and simeprevir for genotype 1 hepatitis C. *ACG Case Rep J* 2015;**3**:42–4.
66. Khuroo MS, Khuroo MS, Khuroo NS. Hepatitis E: discovery, global impact, control and cure. *World J Gastroenterol* 2016;**22**:7030–45.
67. World Health Organization. Hepatitis E vaccine: WHO position paper, May 2015 - recommendations. *Vaccine* 2016;**34**:304–5.
68. European Association for the Study of the Liver. EASL clinical practice guidelines on hepatitis E virus infection. *J Hepatol* 2018;**68**:1256–71.
69. Kamar N, Selves J, Mansuy JM, *et al*. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *N Engl J Med* 2008;**358**:811–7.
70. Senosiaina C, González-Tallón A, López-Sanromán A, *et al*. Hepatitis E seroprevalence in inflammatory bowel disease. *Gastroenterol Hepatol* 2016;**39**:185–90.
71. Guillo L, Uzzan M, Beaugerie L, *et al*. Impact of HIV infection on the course of inflammatory bowel disease and drug safety profile: a multicenter GETAID study. *Clin Gastroenterol Hepatol* 2020;S1542-3565(20)31719-5.
72. Chamberlain FE, Dinani N, Jagjit Singh GK, Bower M, Nelson M. Azathioprine can be safely used in HIV-infected individuals. *AIDS* 2014;**28**:447–8.
73. Gallitano SM, McDermott L, Brar K, Lowenstein E. Use of tumor necrosis factor [TNF] inhibitors in patients with HIV/AIDS. *J Am Acad Dermatol* 2016;**74**:974–80.
74. Fink DL, Hedley L, Miller RF. Systematic review of the efficacy and safety of biological therapy for inflammatory conditions in HIV-infected individuals. *Int J STD AIDS* 2017;**28**:110–9.
75. Byrareddy SN, Arthos J, Cicala C, *et al*. Sustained virologic control in SIV+ macaques after antiretroviral and α4β7 antibody therapy. *Science* 2016;**354**:197–202.
76. Aharoni Golan M, Weisshof R, Wang Y, Rubin DT. New diagnosis of acquired immunodeficiency syndrome in a patient with Crohn's disease. *ACG Case Rep J* 2019;**6**:e00056.
77. Menon K, Van Voorhees AS, Bebo BF Jr, *et al*.; National Psoriasis Foundation. Psoriasis in patients with HIV infection: from the medical board of the National Psoriasis Foundation. *J Am Acad Dermatol* 2010;**62**:291–9.

78. Duvic M, Johnson TM, Rapini RP, Freese T, Brewton G, Rios A. Acquired immunodeficiency syndrome-associated psoriasis and Reiter's syndrome. *Arch Dermatol* 1987;**123**:1622–32.
79. Fatahzadeh M, Schwartz RA. Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management. *J Am Acad Dermatol* 2007;**57**:737–63; quiz 764–6.
80. Gupta R, Warren T, Wald A. Genital herpes. *Lancet* 2007;**370**:2127–37.
81. Seksik P, Cosnes J, Sokol H, Nion-Larmurier I, Gendre JP, Beaugerie L. Incidence of benign upper respiratory tract infections, HSV and HPV cutaneous infections in inflammatory bowel disease patients treated with azathioprine. *Aliment Pharmacol Ther* 2009;**29**:1106–13.
82. Bradford RD, Pettit AC, Wright PW, *et al*. Herpes simplex encephalitis during treatment with tumor necrosis factor-alpha inhibitors. *Clin Infect Dis* 2009;**49**:924–7.
83. Robineau O, Enrico J, Lemaire X, *et al*. Herpes simplex virus meningoencephalitis in a patient with Crohn's disease on azathioprine therapy. *Am J Gastroenterol* 2010;**105**:240–1.
84. Berger JR, Houff S. Neurological complications of herpes simplex virus type 2 infection. *Arch Neurol* 2008;**65**:596–600.
85. Taplitz RA, Jordan MC. Pneumonia caused by herpesviruses in recipients of hematopoietic cell transplants. *Semin Respir Infect* 2002;**17**:121–9.
86. Shale MJ, Seow CH, Coffin CS, Kaplan GG, Panaccione R, Ghosh S. Review article: chronic viral infection in the anti-tumour necrosis factor therapy era in inflammatory bowel disease. *Aliment Pharmacol Ther* 2010;**31**:20–34.
87. Schunter MO, Walles T, Fritz P, *et al*. Herpes simplex virus colitis complicating ulcerative colitis: a case report and brief review on superinfections. *J Crohns Colitis* 2007;**1**:41–6.
88. Blaszyk H, Hyman NH, Cooper K. Herpes simplex virus colitis in ulcerative colitis, simulating malignancy. *Histopathology* 2006;**49**:316–8.
89. Martinez V, Caumes E, Chosidow O. Treatment to prevent recurrent genital herpes. *Curr Opin Infect Dis* 2008;**21**:42–8.
90. Nugent Z, Singh H, Targownik LE, Bernstein CN. Herpes zoster infection and herpes zoster vaccination in a population-based sample of persons with IBD: is there still an unmet need? *Inflamm Bowel Dis* 2019;**25**:532–40.
91. Khan N, Trivedi C, Kavani H, Medvedeva E, Lewis J, Yang YX. Efficacy of live attenuated herpes zoster vaccine in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2019;**17**:1341–7.
92. Khan N, Shah Y, Trivedi C, Lewis JD. Safety of herpes zoster vaccination among inflammatory bowel disease patients being treated with anti-TNF medications. *Aliment Pharmacol Ther* 2017;**46**:668–72.
93. Wasan SK, Zullow S, Berg A, Cheifetz AS, Ganley-Leal L, Farraye FA. Herpes zoster vaccine response in inflammatory bowel disease patients on low-dose immunosuppression. *Inflamm Bowel Dis* 2016;**22**:1391–6.
94. Calabrese LH, Abud-Mendoza C, Lindsey SM, *et al*. Live zoster vaccine in patients with rheumatoid arthritis treated with tofacitinib with or without methotrexate, or adalimumab with methotrexate: a post hoc analysis of data from a phase IIIb/IV randomised study. *Arthritis Care Res* 2020;**72**:353–9.
95. Grint DJ, McDonald HI, Walker JL, Amirthalingam G, Andrews N, Thomas S. Safety of inadvertent administration of live zoster vaccine to immunosuppressed individuals in a UK-based observational cohort analysis. *BMJ Open* 2020;**10**:e034886.
96. Lal H, Cunningham AL, Godeaux O, *et al*.; ZOE-50 Study Group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med* 2015;**372**:2087–96.
97. Dagnew AF, Rausch D, Hervé C, Zahaf T, Levin MJ, Schuind A; ZOE-50/70 study group. Efficacy and serious adverse events profile of the adjuvanted recombinant zoster vaccine in adults with pre-existing potential immune-mediated diseases: a pooled post hoc analysis on two parallel randomised trials. *Rheumatology* 2021;**60**:1226–33.
98. Winston DJ, Mullane KM, Cornely OA, *et al*.; V212 Protocol 001 Trial Team. Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: an international, multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2018;**391**:2116–27.
99. Kochhar G, D A, Caldera F, Farraye F. Effectiveness of recombinant zoster vaccine [RZV] in immunosuppressed patients with inflammatory bowel disease: a population based analysis. 2000:DDW.
100. Winthrop KL, Melmed GY, Vermeire S, *et al*. Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. *Inflamm Bowel Dis* 2018;**24**:2258–65.
101. www.ema.europa.eu/en/medicines/human/EPAR/shingrix.
102. Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG clinical guideline: preventive care in inflammatory bowel disease. *Am J Gastroenterol* 2017;**112**:241–58.
103. Caldera F, Wasan SK, Farraye FA, Hayney MS. Caution when assessing immunity to varicella through antibody testing in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2017;**23**:E50–1.
104. Rubin LG, Levin MJ, Ljungman P, *et al*.; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014;**58**:e44–100.
105. Beswick L, Ye B, van Langenberg DR. Toward an algorithm for the diagnosis and management of CMV in patients with colitis. *Inflamm Bowel Dis* 2016;**22**:2966–76.
106. Cohen S, Martinez-Vinson C, Aloi M, *et al*.; Pediatric IBD Porto Group of ESPGHAN. Cytomegalovirus infection in pediatric severe ulcerative colitis - a multicenter study from the pediatric inflammatory bowel disease Porto group of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. *Pediatr Infect Dis J* 2018;**37**:197–201.
107. Kim YS, Kim YH, Kim JS, *et al*. Long-term outcomes of cytomegalovirus reactivation in patients with moderate to severe ulcerative colitis: a multicenter study. *Gut Liver* 2014;**8**:643–7.
108. Schenk W, Klugmann T, Borkenhagen A, *et al*. The detection of the cytomegalovirus DNA in the colonic mucosa of patients with ulcerative colitis is associated with increased long-term risk of proctocolectomy: results from an outpatient IBD clinic. *Int J Colorectal Dis* 2019;**34**:393–400.
109. Lee HS, Park SH, Kim SH, *et al*. Risk factors and clinical outcomes associated with cytomegalovirus colitis in patients with acute severe ulcerative colitis. *Inflamm Bowel Dis* 2016;**22**:912–8.
110. Criscuoli V, Rizzuto MR, Gallo E, Orlando A, Cottone M. Toxic megacolon and human Cytomegalovirus in a series of severe ulcerative colitis patients. *J Clin Virol* 2015;**66**:103–6.
111. Matsumoto S, Yoshida Y. What are the factors that affect hospitalization and surgery for aggravation of ulcerative colitis? *Eur J Gastroenterol Hepatol* 2014;**26**:282–7.
112. Oh SJ, Lee CK, Kim YW, *et al*. True cytomegalovirus colitis is a poor prognostic indicator in patients with ulcerative colitis flares: the 10-year experience of an academic referral inflammatory bowel disease center. *Scand J Gastroenterol* 2019;**54**:976–83.
113. Zhang WX, Ma CY, Zhang JG, *et al*. Effects of cytomegalovirus infection on the prognosis of inflammatory bowel disease patients. *Exp Ther Med* 2016;**12**:3287–93.
114. McCurdy JD, Jones A, Enders FT, *et al*. A model for identifying cytomegalovirus in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2015;**13**:131–7.
115. Nowacki TM, Bettenworth D, Meister T, *et al*. Novel score predicts risk for cytomegalovirus infection in ulcerative colitis. *J Clin Virol* 2018;**105**:103–8.
116. Henmi Y, Kakimoto K, Inoue T, *et al*. Cytomegalovirus infection in ulcerative colitis assessed by quantitative polymerase chain reaction: risk factors and effects of immunosuppressants. *J Clin Biochem Nutr* 2018;**63**:246–51.
117. Tun GSZ, Raza M, Hale MF, Lobo AJ. Polymerase chain reaction for detection of mucosal cytomegalovirus infection in patients with acute ulcerative colitis. *Ann Gastroenterol* 2019;**32**:81–7.
118. Liu CC, Ji S, Ding Y, Zhou L, Liu X, Li W. Cytomegalovirus infection and steroid-refractory inflammatory bowel disease: possible relationship from an updated meta-analysis. *Ir J Med Sci* 2018;**187**:935–42.
119. Lv YL, Han FF, Jia YJ, *et al*. Is cytomegalovirus infection related to inflammatory bowel disease, especially steroid-resistant inflammatory bowel disease? A meta-analysis. *Infect Drug Resist* 2017;**10**:511–9.
120. Wu XW, Wu L, Ji HZ, Wang FY. Relationship between cytomegalovirus infection and steroid resistance in inflammatory bowel disease: a meta-analysis. *Dig Dis Sci* 2015;**60**:3203–8.
121. Tandon P, James P, Cordeiro E, *et al*. Diagnostic accuracy of blood-based tests and histopathology for cytomegalovirus reactivation in

inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2017;**23**:551–60.
122. Kotton CN, Kumar D, Caliendo AM, *et al*.; Transplantation Society International CMV Consensus Group. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* 2013;**96**:333–60.
123. Emery V, Zuckerman M, Jackson G, *et al*. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. *Br J Haematol* 2013;**162**:25–39.
124. Kim JW, Boo SJ, Ye BD, *et al*. Clinical utility of cytomegalovirus antigenaemia assay and blood cytomegalovirus DNA PCR for cytomegaloviral colitis patients with moderate to severe ulcerative colitis. *J Crohns Colitis* 2014;**8**:693–701.
125. Roblin X, Pillet S, Oussalah A, *et al*. Cytomegalovirus load in inflamed intestinal tissue is predictive of resistance to immunosuppressive therapy in ulcerative colitis. *Am J Gastroenterol* 2011;**106**:2001–8.
126. Zidar N, Ferkolj I, Tepeš K, *et al*. Diagnosing cytomegalovirus in patients with inflammatory bowel disease – by immunohistochemistry or polymerase chain reaction? *Virchows Arch* 2015;**466**:533–9.
127. McCurdy JD, Enders FT, Jones A, *et al*. Detection of cytomegalovirus in patients with inflammatory bowel disease: where to biopsy and how many biopsies? *Inflamm Bowel Dis* 2015;**21**:2833–8.
128. Johnson J, Affolter K, Boynton K, Chen X, Valentine J, Peterson K. CMV disease in IBD: comparison of diagnostic tests and correlation with disease outcome. *Inflamm Bowel Dis* 2018;**24**:1539–46.
129. Mourad FH, Hashash J, Kariyawasam VC, Leong RW, Ulcerative colitis and cytomegalovirus infection: from A to Z. *J Crohns Colitis* 2020;**8**:14.
130. Inokuchi T, Kato J, Hiraoka S, *et al*. Long-term follow-up of ulcerative colitis patients treated on the basis of their cytomegalovirus antigen status. *World J Gastroenterol* 2014;**20**:509–17.
131. Rawa-Gołębiewska A, Lenarcik M, Zagórowicz E. Resolution of CMV infection in the bowel on vedolizumab therapy. *J Crohns Colitis* 2019;**13**:1234–5.
132. Hommel C, Pillet S, Rahier JF. Comment on: 'Resolution of CMV infection in the bowel on vedolizumab therapy'. *J Crohns Colitis* 2020;**14**:148–9.
133. Bontà J, Zeitz J, Frei P, *et al*. Cytomegalovirus disease in inflammatory bowel disease: epidemiology and disease characteristics in a large single-centre experience. *Eur J Gastroenterol Hepatol* 2016;**28**:1329–34.
134. Ciccocioppo R, Racca F, Paolucci S, *et al*. Human cytomegalovirus and Epstein-Barr virus infection in inflammatory bowel disease: need for mucosal viral load measurement. *World J Gastroenterol* 2015;**21**:1915–26.
135. Clos-Parals A, Rodríguez-Martínez P, Cañete F, *et al*. Prognostic value of the burden of cytomegalovirus colonic reactivation evaluated by immunohistochemical staining in patients with active ulcerative colitis. *J Crohns Colitis* 2019;**13**:385–8.
136. Delvincourt M, Lopez A, Pillet S, *et al*. The impact of cytomegalovirus reactivation and its treatment on the course of inflammatory bowel disease. *Aliment Pharmacol Ther* 2014;**39**:712–20.
137. do Carmo AM, Santos F, Ortiz-Agostinho CL, *et al*. Cytomegalovirus infection in inflammatory bowel disease is not associated with worsening of intestinal inflammatory activity. *PLoS One* 2015;**10**:e0133102.
138. Hirayama Y, Ando T, Hirooka Y, *et al*. Characteristic endoscopic findings and risk factors for cytomegalovirus-associated colitis in patients with active ulcerative colitis. *World J Gastrointest Endosc* 2016;**8**:301–9.
139. Kopylov U, Papamichael K, Katsanos K, *et al*. Impact of infliximab and cyclosporine on the risk of colectomy in hospitalized patients with ulcerative colitis complicated by cytomegalovirus- a multicenter retrospective study. *Inflamm Bowel Dis* 2017;**23**:1605–13.
140. Ormeci AC, Akyuz F, Baran B, *et al*. Steroid-refractory inflammatory bowel disease is a risk factor for CMV infection. *Eur Rev Med Pharmacol Sci* 2016;**20**:858–65.
141. Levin A, Yaari S, Stoff R, Caplan O, Wolf DG, Israeli E. Diagnosis of cytomegalovirus infection during exacerbation of ulcerative colitis. *Digestion* 2017;**96**:142–8.
142. Torres P, Lobatón T, Cañete F, *et al*. Cytomegalovirus primoinfection in inflammatory bowel disease. *Gastroenterol Hepatol* 2018;**41**:453–4.
143. Fakhreddine AY, Frenette CT, Konijeti GG. A practical review of cytomegalovirus in gastroenterology and hepatology. *Gastroenterol Res Pract* 2019;**2019**:6156581.
144. Kopylov U, Eliakim-Raz N, Szilagy A, Seidman E, Ben-Horin S, Katz L. Antiviral therapy in cytomegalovirus-positive ulcerative colitis: a systematic review and meta-analysis. *World J Gastroenterol* 2014;**20**:2695–703.
145. Shukla T, Singh S, Loftus EV Jr, Bruining DH, McCurdy JD. Antiviral therapy in steroid-refractory ulcerative colitis with cytomegalovirus: systematic review and meta-analysis. *Inflamm Bowel Dis* 2015;**21**:2718–25.
146. Jones A, McCurdy JD, Loftus EV Jr, *et al*. Effects of antiviral therapy for patients with inflammatory bowel disease and a positive intestinal biopsy for cytomegalovirus. *Clin Gastroenterol Hepatol* 2015;**13**:949–55.
147. Zagórowicz E, Bugajski M, Wieszczy P, Pietrzak A, Magdziak A, Mróz A. Cytomegalovirus infection in ulcerative colitis is related to severe inflammation and a high count of cytomegalovirus-positive cells in biopsy is a risk factor for colectomy. *J Crohns Colitis* 2016;**10**:1205–11.
148. de Francisco R, Castaño-García A, Martínez-González S, *et al*. Impact of Epstein-Barr virus serological status on clinical outcomes in adult patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2018;**48**:723–30.
149. Gordon J, Ramaswami A, Beuttler M, *et al*. EBV status and thiopurine use in pediatric IBD. *J Pediatr Gastroenterol Nutr* 2016;**62**:711–4.
150. Macsween KF, Crawford D. Epstein-Barr virus—recent advances. *Lancet Infect Dis* 2003;**3**:131–40.
151. Thorley-Lawson DA. EBV the prototypical human tumor virus—just how bad is it? *J Allergy Clin Immunol* 2005;**116**:251–61.
152. Honkila M, Niinimäki R, Taskinen M, *et al*. A nearly fatal primary Epstein-Barr virus infection associated with low NK-cell counts in a patient receiving azathioprine: a case report and review of literature. *BMC Infect Dis* 2019;**19**:404.
153. Thompson G, Pepperell D, Lawrence I, McGettigan BD. Crohn's disease complicated by Epstein-Barr virus-driven haemophagocytic lymphohistiocytosis successfully treated with rituximab. *BMJ Case Rep* 2017. Doi: bcr2016218578.
154. Goetgebuer RL, van der Woude CJ, de Ridder L, Doukas M, de Vries AC. Clinical and endoscopic complications of Epstein-Barr virus in inflammatory bowel disease: an illustrative case series. *Int J Colorectal Dis* 2019;**34**:923–6.
155. Virdis F, Tacci S, Messina F, Varcada M. Hemophagocytic lymphohistiocytosis caused by primary Epstein-Barr virus in patient with Crohn's disease. *World J Gastrointest Surg* 2013;**5**:306–8.
156. Magro F, Santos-Antunes J, Albuquerque A, *et al*. Epstein-Barr virus in inflammatory bowel disease - correlation with different therapeutic regimens. *Inflamm Bowel Dis* 2013;**19**:1710–6.
157. Linton MS, Kroeker K, Fedorak D, Dieleman L, Fedorak RN. Prevalence of Epstein-Barr Virus in a population of patients with inflammatory bowel disease: a prospective cohort study. *Aliment Pharmacol Ther* 2013;**38**:1248–54.
158. Rathore R, Tomlinson K, Dukka H, Farrugia D, Lambie M, Incidence, recurrence and survival post chemotherapy in renal transplant recipients with post transplant lymphoproliferative disorder: single center study. *Am J Transplant* 2017.
159. Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. *Clin Cancer Res* 2004;**10**:803–21.
160. Dayharsh GA, Loftus EV Jr, Sandborn WJ, *et al*. Epstein-Barr virus-positive lymphoma in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. *Gastroenterology* 2002;**122**:72–7.
161. Winnicki M, Gariepy G, Sauthier PG, Funaro D. Hodgkin lymphoma presenting as a vulvar mass in a patient with Crohn disease: a case report and literature review. *J Low Genit Tract Dis* 2009;**13**:110–4.
162. Van Biervliet S, Velde SV, De Bruyne R, De Looze D, De Vos M, Van Winckel M. Epstein-Barr virus related lymphoma in inflammatory bowel disease. *Acta Gastroenterol Belg* 2008;**71**:33–5.
163. Moran NR, Webster B, Lee KM, *et al*. Epstein Barr virus-positive mucocutaneous ulcer of the colon associated Hodgkin lymphoma in Crohn's disease. *World J Gastroenterol* 2015;**21**:6072–6.

164. Glesner MK, Ocias L, Larsen TS, Pedersen C. Primary CNS lymphoma in a patient treated with azathioprine. *BMJ Case Rep* 2014;2014:bcr2014205108.
165. Altaf S, Atreaga G, Joshi AY, Rodriguez V, Diffuse large B-cell lymphoma in an adolescent female presenting with Epstein-Barr virus-driven hemophagocytic lymphohistiocytosis: a case report. *J Med Case Rep* 2012;**6**:141.
166. Speckmann C, Lehmberg K, Albert MH, *et al*. X-linked inhibitor of apoptosis [XIAP] deficiency: the spectrum of presenting manifestations beyond hemophagocytic lymphohistiocytosis. *Clin Immunol* 2013;**149**:133–41.
167. Biank VF, Sheth MK, Talano J, *et al*. Association of Crohn's disease, thiopurines, and primary Epstein-Barr virus infection with hemophagocytic lymphohistiocytosis. *J Pediatr* 2011;**159**:808–12.
168. Au JK, Said JW, Sepahdari AR, St John MA. Head and neck Epstein-Barr virus mucocutaneous ulcer: case report and literature review. *Laryngoscope* 2016;**126**:2500–4.
169. Dojcinov SD, Venkataraman G, Raffeld M, Pittaluga S, Jaffe ES. EBV positive mucocutaneous ulcer – a study of 26 cases associated with various sources of immunosuppression. *Am J Surg Pathol* 2010;**34**:405–17.
170. Juan A, Lobatón T, Tapia G, Mañosa M, Cabré E, Domènech E. Epstein-Barr virus-positive mucocutaneous ulcer in Crohn's disease. A condition to consider in immunosuppressed IBD patients. *Dig Liver Dis* 2017;**49**:934–7.
171. Matnani R, Peker D. Azathioprine induced Epstein Barr virus-positive mucocutaneous ulcer arising in perianal fistula and abscess associated with Crohn's disease. *J Crohns Colitis* 2014;**8**:1747–8.
172. Hamanaka S, Nakagawa T, Ota S, *et al*. Immunomodulator-associated Epstein-Barr virus-positive mucocutaneous ulcer in a patient with refractory Crohn's disease. *Clin J Gastroenterol* 2019;**12**:330–5.
173. Tinsley A, Navabi S, Williams ED, *et al*. Increased risk of influenza and influenza-related complications among 140,480 patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2019;**25**:369–76.
174. Naganuma M, Fujii T, Kunisaki R, *et al*. Incidence and characteristics of the 2009 influenza [H1N1] infections in inflammatory bowel disease patients. *J Crohns Colitis* 2013;**7**:308–13.
175. Van Kerkhove MD, Vandemaele KA, Shinde V, *et al*.; WHO Working Group for Risk Factors for Severe H1N1pdm Infection. Risk factors for severe outcomes following 2009 influenza A [H1N1] infection: a global pooled analysis. *PLoS Med* 2011;**8**:e1001053.
176. Rahier JF, Papay P, Salleron J, *et al*. Influenza A [H1N1]v infection in patients with inflammatory bowel disease: a case series. *Aliment Pharmacol Ther* 2011;**33**:499–500.
177. Grohskopf LA, Alyanak E, Broder KR, *et al*. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on immunization practices - United States, 2020-21 influenza season. *MMWR Recomm Rep* 2020;**69**:1–24.
178. Narula N, Dhillon AS, Chauhan U, Marshall JK. An audit of influenza vaccination status in adults with inflammatory bowel disease. *Can J Gastroenterol* 2012;**26**:593–6.
179. Crawford NW, Catto-Smith AG, Oliver MR, Cameron DJ, Buttery JP. An Australian audit of vaccination status in children and adolescents with inflammatory bowel disease. *BMC Gastroenterol* 2011;**11**:87.
180. Boltin D, Gingold-Belfer R, Kimchi NA, Ben-Bassat O, Niv Y, Birkenfeld S. Utilization of influenza immunization in adults with Crohn's disease - a longitudinal, population-based study. *Inflamm Bowel Dis* 2014;**20**:240–5.
181. Coenen S, Weyts E, Jorissen C, *et al*. Effects of education and information on vaccination behavior in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2017;**23**:318–24.
182. Reich JS, Miller HL, Wasan SK, *et al*. Influenza and pneumococcal vaccination rates in patients with inflammatory bowel disease. *Gastroenterol Hepatol* 2015;**11**:396–401.
183. Sitte J, Frentiu E, Baumann C, *et al*. Vaccination for influenza and pneumococcus in patients with gastrointestinal cancer or inflammatory bowel disease: a prospective cohort study of methods for improving coverage. *Aliment Pharmacol Ther* 2019;**49**:84–90.
184. Andrisani G, Frasca D, Romero M, *et al*. Immune response to influenza A/H1N1 vaccine in inflammatory bowel disease patients treated with anti TNF-α agents: effects of combined therapy with immunosuppressants. *J Crohns Colitis* 2013;**7**:301–7.
185. Cullen G, Bader C, Korzenik JR, Sands BE. Serological response to the 2009 H1N1 influenza vaccination in patients with inflammatory bowel disease. *Gut* 2012;**61**:385–91.
186. deBruyn JC, Hilsden R, Fonseca K, *et al*. Immunogenicity and safety of influenza vaccination in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**18**:25–33.
187. Hagihara Y, Ohfuji S, Watanabe K, *et al*. Infliximab and/or immunomodulators inhibit immune responses to trivalent influenza vaccination in adults with inflammatory bowel disease. *J Crohns Colitis* 2014;**8**:223–33.
188. Mamula P, Markowitz JE, Piccoli DA, Klimov A, Cohen L, Baldassano RN. Immune response to influenza vaccine in pediatric patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007;**5**:851–6.
189. Lu Y, Jacobson DL, Ashworth LA, *et al*. Immune response to influenza vaccine in children with inflammatory bowel disease. *Am J Gastroenterol* 2009;**104**:444–53.
190. deBruyn J, Fonseca K, Ghosh S, *et al*. Immunogenicity of influenza vaccine for patients with inflammatory bowel disease on maintenance infliximab therapy: a randomised trial. *Inflamm Bowel Dis* 2016;**22**:638–47.
191. Launay O, Abitbol V, Krivine A, *et al*.; MICIVAX Study Group. Immunogenicity and safety of influenza vaccine in inflammatory bowel disease patients treated or not with immunomodulators and/or biologics: a 2-year prospective study. *J Crohns Colitis* 2015;**9**:1096–107.
192. Winthrop KL, Bingham CO 3rd, Komocsar WJ, *et al*. Evaluation of pneumococcal and tetanus vaccine responses in patients with rheumatoid arthritis receiving baricitinib: results from a long-term extension trial substudy. *Arthritis Res Ther* 2019;**21**:102.
193. Winthrop KL, Silverfield J, Racewicz A, *et al*. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis* 2016;**75**:687–95.
194. Caldera F, Hillman L, Saha S, *et al*. Immunogenicity of high dose influenza vaccine for patients with inflammatory bowel disease on anti-TNF monotherapy: a randomized clinical trial. *Inflamm Bowel Dis* 2020;**26**:593–602.
195. Park JK, Lee YJ, Shin K, *et al*. Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomized clinical trial. *Ann Rheum Dis* 2018;**77**:898–904.
196. Matsumoto H, Ohfuji S, Watanabe K, *et al*. Booster influenza vaccination does not improve immune response in adult inflammatory bowel disease patients treated with immunosuppressives: a randomized controlled trial. *J Gastroenterol* 2015;**50**:876–86.
197. Shirai S, Hara M, Sakata Y, *et al*. Immunogenicity of quadrivalent influenza vaccine for patients with inflammatory bowel disease undergoing immunosuppressive therapy. *Inflamm Bowel Dis* 2018;**24**:1082–91.
198. Rahier JF, Papay P, Salleron J, *et al*.; European Crohn's and Colitis Organisation [ECCO]. H1N1 vaccines in a large observational cohort of patients with inflammatory bowel disease treated with immunomodulators and biological therapy. *Gut* 2011;**60**:456–62.
199. Cullen G, Baden RP, Cheifetz AS. Varicella zoster virus infection in inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**18**:2392–403.
200. Goel K, Bunker M, Balog A, Silverman JF, Fulminant herpes simplex hepatitis secondary to adalimumab in Crohn's disease: a case report. *Clin Med Insights Case Rep* 2019;**12**:1–4.
201. Golds G, Worobetz L. Fulminant hepatic failure in a patient with Crohn's disease on infliximab possibly related to reactivation of herpes simplex virus 2 infection. *Case Reports Hepatol* 2016;**2016**:2132056.
202. Haag LM, Hofmann J, Kredel LI, *et al*. Herpes simplex virus sepsis in a young woman with Crohn's disease. *J Crohns Colitis* 2015;**9**:1169–73.
203. Khan N, Patel D, Trivedi C, *et al*. Overall and comparative risk of herpes zoster with pharmacotherapy for inflammatory bowel diseases: a nationwide cohort study. *Clin Gastroenterol Hepatol* 2018;**16**:1919–27.e3.

204. Misin A, Antonello R, Di Bella S, *et al*. Measles: an overview of a re-emerging disease in children and immunocompromised patients. *Microorganisms* 2020;**8**:276.
205. Cohen RE, Salem M, Ha C. Managing immunosuppressed patients with inflammatory bowel disease during a measles outbreak. *Am J Gastroenterol* 2019;**114**:1563–5.
206. Servet-Delprat C, Vidalain PO, Valentin H, Rabourdin-Combe C. Measles virus and dendritic cell functions: how specific response cohabits with immunosuppression. *Curr Top Microbiol Immunol* 2003;**276**:103–23.
207. Uyeki TM, Bernstein H, Bradley JS. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis* 2019;**68**:e1–47.
208. Marehbian J, Arrighi M, Hass S, Tian H, Sandborn W, Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. *Am J Gastroenterol* 2009;**104**:2524–33.
209. Centers for Disease Control and Prevention. *Sexually Transmitted Diseases Treatment Guidelines*, 2015. https://www.cdc.gov/std/tg2015/.
210. Kusne S, Schwartz M, Breinig MK, *et al*. Herpes simplex virus hepatitis after solid organ transplantation in adults. *J Infect Dis* 1991;**163**:1001–7.
211. Martin-Gandul C, Stampf S, Héquet D, *et al*.; Swiss Transplant Cohort Study [STCS]. Preventive strategies against cytomegalovirus and incidence of α-herpes virus infections in solid organ transplant recipients: a nationwide cohort study. *Am J Transplant* 2017;**17**:1813–22.
212. Siegal FP, Lopez C, Hammer GS, *et al*. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med* 1981;**305**:1439–44.
213. Erard V, Wald A, Corey L, Leisenring WM, Boeckh M. Use of long-term suppressive acyclovir after hematopoietic stem-cell transplantation: impact on herpes simplex virus [HSV] disease and drug-resistant HSV disease. *J Infect Dis* 2007;**196**:266–70.
214. Szenborn L, Kraszewska-Głomba B, Jackowska T, *et al*. Polish Consensus guidelines on the use of acyclovir in the treatment and prevention of VZV and HSV infections. *J Infect Chemother* 2016;**22**:65–71.
215. Cohen JI. Clinical practice: herpes zoster. *N Engl J Med* 2013;**369**:255–63.
216. Côté-Daigneault J, Peerani F, MacMahon E, Delaporte E, Rahier JF, Colombel JF. Management and prevention of herpes zoster in the immunocompromised inflammatory bowel disease patient: a clinical quandary. *Inflamm Bowel Dis* 2016;**22**:2538–47.
217. Dworkin RH, Johnson RW, Breuer J, *et al*. Recommendations for the management of herpes zoster. *Clin Infect Dis* 2007;**44[Suppl 1]**:S1–26.
218. Harpaz R, Ortega-Sanchez I, Seward JF; Advisory Committee on Immunization Practices [ACIP], Centers for Disease Control and Prevention [CDC]. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR Recomm Rep* 2008;**57**:1–30.
219. Colombel JF. Herpes zoster in patients receiving JAK inhibitors for ulcerative colitis: mechanism, epidemiology, management, and prevention. *Inflamm Bowel Dis* 2018;**24**:2173–82.
220. Li M, Yang QF, Cao Q, *et al*. High-risk human papilloma virus infection and cervical neoplasm in female inflammatory bowel disease patients: a cross-sectional study. *Gastroenterol Rep* 2019;**7**:338–44.
221. Rungoe C, Simonsen J, Riis L, *et al*. Inflammatory bowel disease and cervical neoplasia: a population-based nationwide cohort study. *Clin Gastroenterol Hepatol* 2015;**13**:693–700.e1.
222. Dugué PA, Rebolj M, Hallas J, Garred P, Lynge E. Risk of cervical cancer in women with autoimmune diseases, in relation with their use of immunosuppressants and screening: population-based cohort study. *Int J Cancer* 2015;**136**:E711–9.
223. Singh H, Demers AA, Nugent Z, Mahmud SM, Kliewer EV, Bernstein CN. Risk of cervical abnormalities in women with inflammatory bowel disease: a population-based nested case-control study. *Gastroenterology* 2009;**136**:451–8.
224. Luthra P, Peyrin-Biroulet L, Ford AC. Systematic review and meta-analysis: opportunistic infections and malignancies during treatment with anti-integrin antibodies in inflammatory bowel disease. *Aliment Pharmacol Ther* 2015;**41**:1227–36.
225. de Sanjose S, Quint WG, Alemany L, *et al*.; Retrospective International Survey and HPV Time Trends Study Group. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol* 2010;**11**:1048–56.
226. Workowski KA, Bolan G. Sexually transmitted diseases treatment guidelines, 2015. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2015;**64**:1–137.
227. Moscicki AB, Flowers L, Huchko MJ, *et al*. Guidelines for cervical cancer screening in immunosuppressed women without HIV infection. *J Low Genit Tract Dis* 2019;**23**:87–101.
228. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2019;**68**:698–702.
229. Jacobson DL, Bousvaros A, Ashworth L, *et al*. Immunogenicity and tolerability to human papillomavirus-like particle vaccine in girls and young women with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;**19**:1441–9.
230. Mok CC, Ho LY, Fong LS, To CH. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. *Ann Rheum Dis* 2013;**72**:659–64.
231. Mok CC, Ho LY, To CH. Long-term immunogenicity of a quadrivalent human papillomavirus vaccine in systemic lupus erythematosus. *Vaccine* 2018;**36**:3301–7.
232. Soybilgic A, Onel KB, Utset T, Alexander K, Wagner-Weiner L. Safety and immunogenicity of the quadrivalent HPV vaccine in female Systemic Lupus Erythematosus patients aged 12 to 26 years. *Pediatr Rheumatol Online J* 2013;**11**:29.
233. Heijstek MW, Scherpenisse M, Groot N, *et al*. Immunogenicity and safety of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis: a prospective controlled observational cohort study. *Ann Rheum Dis* 2014;**73**:1500–7.
234. Esposito S, Corona F, Barzon L, *et al*. Immunogenicity, safety and tolerability of a bivalent human papillomavirus vaccine in adolescents with juvenile idiopathic arthritis. *Expert Rev Vaccines* 2014;**13**:1387–93.
235. Cohen RD, Bhayat F, Blake A, Travis S. The safety profile of vedolizumab in ulcerative colitis and Crohn's disease: 4 years of global post-marketing data. *J Crohns Colitis* 2020;**14**:192–204.
236. Taxonera C, Sagastagoitia I, Alba C, Mañas N, Olivares D, Rey E. 2019 novel coronavirus disease [COVID-19] in patients with inflammatory bowel diseases. *Aliment Pharmacol Ther* 2020;**52**:276–83.
237. Allocca M, Fiorino G, Zallot C, *et al*. Incidence and patterns of COVID-19 among inflammatory bowel disease patients from the Nancy and Milan cohorts. *Clin Gastroenterol Hepatol* 2020;**18**:2134–5.
238. An P, Ji M, Ren H, *et al*. Prevention of COVID-19 in patients with inflammatory bowel disease in Wuhan, China. *Lancet Gastroenterol Hepatol* 2020;**5**:525–7.
239. Ungaro RC, Brenner EJ, Gearry RB, *et al*. Effect of IBD medications on COVID-19 outcomes: results from an international registry. *Gut* 2021;**70**:725–32.
240. Bezzio C, Saibeni S, Variola A, *et al*.; Italian Group for the Study of Inflammatory Bowel Disease [IG-IBD]. Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. *Gut* 2020;**69**:1213–7.
241. Lin L, Jiang X, Zhang Z, *et al*. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut* 2020;**69**:997–1001.
242. Magro F, Rahier JF, Abreu C, *et al*. Inflammatory bowel disease management during the COVID-19 outbreak: the 10 do's and don'ts from the ECCO-COVID taskforce. *J Crohns Colitis* 2020;**14**:798–806.
243. Rodríguez-Lago I, Ramírez de la Piscina P, Elorza A, Merino O, Ortiz de Zárate J, Cabriada JL. Characteristics and prognosis of patients with inflammatory bowel disease during the SARS-CoV-2 pandemic in the Basque Country [Spain]. *Gastroenterology* 2020;**159**:781–3.
244. Din S, Kent A, Pollok RC, *et al*. Adaptations to the British Society of Gastroenterology guidelines on the management of acute severe UC in the context of the COVID-19 pandemic: a RAND appropriateness panel. *Gut* 2020;**69**:1769–77.

245. Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. *Nat Rev Immunol* 2020;**20**:615–32.
246. World Health Organization. *Draft Landscape of COVID-19 Candidate Vaccines*, 2020. Geneva: WHO; 2020.
247. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-achieve-first-authorization-world.
248. https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html.
249. https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-primary-efficacy-analysis-phase-3-cove-study.
250. https://www.nhs.uk/conditions/coronavirus-covid-19/coronavirus-vaccination/coronavirus-vaccine/?gclid=EAIaIQobChMIvIiEo7O_7QIVlO7tCh1LcQxfEAAYASAAEgKbAfD_BwE.
251. Siegel CA, Melmed GY, McGovern DP, *et al.*; International Organization for the Study of Inflammatory Bowel Disease [IOIBD]; International Organization for the Study of Inflammatory Bowel Diseases [IOIBD]. SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut* 2021;**70**:635–40.
252. Alexander JL, Moran GW, Gaya DR, *et al.*; Inflammatory Bowel Disease section of the British Society of Gastroenterology, and the Inflammatory Bowel Disease Clinical Research Group. SARS-CoV-2 vaccination for patients with inflammatory bowel disease: a British Society of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group position statement. *Lancet Gastroenterol Hepatol* 2021;**6**:218–24.
253. Latorre I, Mínguez S, Carrascosa JM, *et al.* Immune-mediated inflammatory diseases differently affect IGRAs' accuracy for latent tuberculosis infection diagnosis in clinical practice. *PLoS One* 2017;**12**:e0189202.
254. Wong SH, Gao Q, Tsoi KK, *et al.* Effect of immunosuppressive therapy on interferon γ release assay for latent tuberculosis screening in patients with autoimmune diseases: a systematic review and meta-analysis. *Thorax* 2016;**71**:64–72.
255. Wong SH, Ip M, Tang W, *et al.* Performance of interferon-gamma release assay for tuberculosis screening in inflammatory bowel disease patients. *Inflamm Bowel Dis* 2014;**20**:2067–72.
256. Bonovas S, Fiorino G, Allocca M, *et al.* Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol* 2016;**14**:1385–97.e10.
257. Singh JA, Wells GA, Christensen R, *et al.* Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011;**2011**:CD008794.
258. Lorenzetti R, Zullo A, Ridola L, *et al.* Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials. *Ann Med* 2014;**46**:547–54.
259. Ng SC, Hilmi IN, Blake A, *et al.* Low frequency of opportunistic infections in patients receiving vedolizumab in clinical trials and post-marketing setting. *Inflamm Bowel Dis* 2018;**24**:2431–41.
260. Tsai TF, Ho V, Song M, *et al.*; PHOENIX 1, PHOENIX 2, ACCEPT, PEARL and Japanese Ustekinumab Study Groups. The safety of ustekinumab treatment in patients with moderate-to-severe psoriasis and latent tuberculosis infection. *Br J Dermatol* 2012;**167**:1145–52.
261. Loftus E, *et al. Comparison of rates of active tuberculosis infection in the phase 2 and 3 clinical trial programs for anti-IL12/23 and anti-TNFS. In: Digestive Disease Week; May 6-9, 2017*; Chicago, IL.
262. Winthrop KL, Park SH, Gul A, *et al.* Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. *Ann Rheum Dis* 2016;**75**:1133–8.
263. Bogas M, Machado P, Mourão AF, *et al.* Methotrexate treatment in rheumatoid arthritis: management in clinical remission, common infection and tuberculosis. Results from a systematic literature review. *Clin Rheumatol* 2010;**29**:629–35.
264. Chen YJ, Wu CY, Shen JL, Chen TT, Chang YT. Association between traditional systemic antipsoriatic drugs and tuberculosis risk in patients with psoriasis with or without psoriatic arthritis: results of a nationwide cohort study from Taiwan. *J Am Acad Dermatol* 2013;**69**:25–33.
265. Cagatay T, Bingol Z, Kıyan E, *et al.* Follow-up of 1887 patients receiving tumor necrosis-alpha antagonists: tuberculin skin test conversion and tuberculosis risk. *Clin Respir J* 2018;**12**:1668–75.
266. Abitbol Y, Laharie D, Cosnes J, *et al.*; GETAID. Negative screening does not rule out the risk of tuberculosis in patients with inflammatory bowel disease undergoing anti-TNF treatment: a descriptive study on the GETAID cohort. *J Crohns Colitis* 2016;**10**:1179–85.
267. Taxonera C, Ponferrada Á, Riestra S, *et al.*; CONVERT study group from GETECCU. Serial tuberculin skin tests improve the detection of latent tuberculosis infection in patients with inflammatory bowel disease. *J Crohns Colitis* 2018;**12**:1270–9.
268. Kedia S, Mouli VP, Kamat N, *et al.* Risk of tuberculosis in patients with inflammatory bowel disease on infliximab or adalimumab is dependent on the local disease burden of tuberculosis: a systematic review and meta-analysis. *Am J Gastroenterol* 2020;**115**:340–9.
269. Taxonera C, Ponferrada Á, Bermejo F, *et al.*; SEGURTB study group from GETECCU. Early tuberculin skin test for the diagnosis of latent tuberculosis infection in patients with inflammatory bowel disease. *J Crohns Colitis* 2017;**11**:792–800.
270. Maaser C, Sturm A, Vavricka SR, *et al.*; European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD. Part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019;**13**:144–64.
271. Broekmans JF, Migliori GB, Rieder HL, *et al.*; World Health Organization, International Union Against Tuberculosis and Lung Disease, and Royal Netherlands Tuberculosis Association Working Group. European framework for tuberculosis control and elimination in countries with a low incidence. Recommendations of the World Health Organization [WHO], International Union Against Tuberculosis and Lung Disease [IUATLD] and Royal Netherlands Tuberculosis Association [KNCV] Working Group. *Eur Respir J* 2002;**19**:765–75.
272. American Thoracic Society. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: controlling tuberculosis in the United States. *Am J Respir Crit Care Med* 2005;**172**:1169–227.
273. Rampton DS. Preventing TB in patients with Crohn's disease needing infliximab or other anti-TNF therapy. *Gut* 2005;**54**:1360–2.
274. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med* 2004;**350**:2060–7.
275. Diel R, Goletti D, Ferrara G, *et al.* Interferon-γ release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. *Eur Respir J* 2011;**37**:88–99.
276. Girardi E, Angeletti C, Puro V, *et al.* Estimating diagnostic accuracy of tests for latent tuberculosis infection without a gold standard among health care workers. *Euro Surveill* 2009;**14**:19373.
277. Yeh YP, Luh DL, Chang SH, Suo J, Chang HJ, Chen TH. Tuberculin reactivity in adults after 50 years of universal Bacille Calmette-Guerin vaccination in Taiwan. *Trans R Soc Trop Med Hyg* 2005;**99**:509–16.
278. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria? *Int J Tuberc Lung Dis* 2006;**10**:1192–204.
279. Obrador A, López San Román A, Muñoz P, Fortún J, Gassull MA; Grupo Español de Trabajo de Enfermedad de Crohn y Colitis Ulcerosa [GETECCU]. [Consensus guideline on tuberculosis and treatment of inflammatory bowel disease with infliximab. Spanish Working Group on Crohn Disease and Ulcerative Colitis]. *Gastroenterol Hepatol* 2003;**26**:29–33.
280. Zabana Y, Domènech E, San Román AL, *et al.* Tuberculous chemoprophylaxis requirements and safety in inflammatory bowel disease patients prior to anti-TNF therapy. *Inflamm Bowel Dis* 2008;**14**:1387–91.
281. Gómez-Reino JJ, Carmona L, Angel Descalzo M; Biobadaser Group. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists

due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum* 2007;**57**:756–61.
282. Hatemi G, Melikoglu M, Fresko I, Masatlioglu S, Tascilar K, Yazici H. Infliximab does not suppress the tuberculin skin test [purified protein derivative]. *J Rheumatol* 2007;**34**:474–80.
283. Cantini F, Nannini C, Niccoli L, *et al*.; SAFEBIO [Italian multidisciplinary task force for screening of tuberculosis before and during biologic therapy]. Guidance for the management of patients with latent tuberculosis infection requiring biologic therapy in rheumatology and dermatology clinical practice. *Autoimmun Rev* 2015;**14**:503–9.
284. Diel R, Loddenkemper R, Niemann S, Meywald-Walter K, Nienhaus A. Negative and positive predictive value of a whole-blood interferon-γ release assay for developing active tuberculosis: an update. *Am J Respir Crit Care Med* 2011;**183**:88–95.
285. Augustynowicz-Kopeć E, Siemion-Szcześniak I, Zabost A, *et al*. Interferon gamma release assays in patients with respiratory isolates of non-tuberculous mycobacteria - a preliminary study. *Pol J Microbiol* 2019;**68**:15–9.
286. Shahidi N, Fu YT, Qian H, Bressler B. Performance of interferon-gamma release assays in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2012;**18**:2034–42.
287. Bélard E, Semb S, Ruhwald M, *et al*. Prednisolone treatment affects the performance of the QuantiFERON gold in-tube test and the tuberculin skin test in patients with autoimmune disorders screened for latent tuberculosis infection. *Inflamm Bowel Dis* 2011;**17**:2340–9.
288. Papay P, Eser A, Winkler S, *et al*. Factors impacting the results of interferon-γ release assay and tuberculin skin test in routine screening for latent tuberculosis in patients with inflammatory bowel diseases. *Inflamm Bowel Dis* 2011;**17**:84–90.
289. Arias-Guillén M, Riestra S, de Francisco R, *et al*. T-cell profiling and the immunodiagnosis of latent tuberculosis infection in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2014;**20**:329–38.
290. Costantino F, de Carvalho Bittencourt M, Rat AC, *et al*. Screening for latent tuberculosis infection in patients with chronic inflammatory arthritis: discrepancies between tuberculin skin test and interferon-γ release assay results. *J Rheumatol* 2013;**40**:1986–93.
291. Hsia EC, Schluger N, Cush JJ, *et al*. Interferon-γ release assay versus tuberculin skin test prior to treatment with golimumab, a human anti-tumor necrosis factor antibody, in patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis. *Arthritis Rheum* 2012;**64**:2068–77.
292. Pai M, Denkinger CM, Kik SV, *et al*. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. *Clin Microbiol Rev* 2014;**27**:3–20.
293. Winthrop KL, Weinblatt ME, Daley CL. You can't always get what you want, but if you try sometimes [with two tests–TST and IGRA–for tuberculosis] you get what you need. *Ann Rheum Dis* 2012;**71**:1757–60.
294. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K; IGRA Expert Committee; Centers for Disease Control and Prevention [CDC]. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. *MMWR Recomm Rep* 2010;**59**:1–25.
295. Mir Viladrich I, Daudén Tello E, Solano-López G, *et al*. Consensus document on prevention and treatment of tuberculosis in patients for biological treatment. *Arch Bronconeumol* 2016;**52**:36–45.
296. Kim HC, Jo KW, Jung YJ, *et al*. Diagnosis of latent tuberculosis infection before initiation of anti-tumor necrosis factor therapy using both tuberculin skin test and QuantiFERON-TB Gold In Tube assay. *Scand J Infect Dis* 2014;**46**:763–9.
297. O'Shea MK, Fletcher TE, Beeching NJ, *et al*. Tuberculin skin testing and treatment modulates interferon-gamma release assay results for latent tuberculosis in migrants. *PLoS One* 2014;**9**:e97366.
298. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, *et al*.; BIOBADASER Group. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum* 2005;**52**:1766–72.
299. Hommes DW, van Deventer SJ. Infliximab therapy in Crohn's disease: safety issues. *Neth J Med* 2003;**61**:100–4.
300. Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. *N Engl J Med* 2002;**347**:1860–6.
301. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society [ATS] and the Centers for Disease Control and Prevention [CDC]. This statement was endorsed by the Council of the Infectious Diseases Society of America. [IDSA], September 1999, and the sections of this statement. *Am J Respir Crit Care Med* 2000;**161**:S221–47.
302. Sterling TR, Villarino ME, Borisov AS, *et al*.; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011;**365**:2155–66.
303. Menzies D, Adjobimey M, Ruslami R, *et al*. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med* 2018;**379**:440–53.
304. Hoofnagle JH, Björnsson ES. Drug-induced liver injury - types and phenotypes. *N Engl J Med* 2019;**381**:264–73.
305. Arundel C, Lewis JH. Drug-induced liver disease in 2006. *Curr Opin Gastroenterol* 2007;**23**:244–54.
306. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999;**281**:1014–8.
307. Vanhoof J, Landewe S, Van Wijngaerden E, Geusens P. High incidence of hepatotoxicity of isoniazid treatment for tuberculosis chemoprophylaxis in patients with rheumatoid arthritis treated with methotrexate or sulfasalazine and anti-tumour necrosis factor inhibitors. *Ann Rheum Dis* 2003;**62**:1241–2.
308. Takeuchi T, Tatsuki Y, Nogami Y, *et al*. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis* 2008;**67**:189–94.
309. British Thoracic Society Standards of Care. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. *Thorax* 2005;**60**:800–5.
310. Goletti D, Parracino MP, Butera O, *et al*. Isoniazid prophylaxis differently modulates T-cell responses to RD1-epitopes in contacts recently exposed to Mycobacterium tuberculosis: a pilot study. *Respir Res* 2007;**8**:5.
311. Kantsø B, Simonsen J, Hoffmann S, Valentiner-Branth P, Petersen AM, Jess T. Inflammatory bowel disease patients are at increased risk of invasive pneumococcal disease: a nationwide Danish cohort study 1977-2013. *Am J Gastroenterol* 2015;**110**:1582–7.
312. Grijalva CG, Chen L, Delzell E, *et al*. Initiation of tumor necrosis factor-α antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *JAMA* 2011;**306**:2331–9.
313. Case DJ, Copeland LA, Stock EM, Herrera HR, Pfanner TP. Pneumococcal vaccination rates in VHA patients with inflammatory bowel disease. *Medicine [Baltimore]* 2015;**94**:e417.
314. Kantsø B, Halkjær SI, Østergaard Thomsen O, *et al*. Persistence of antibodies to pneumococcal conjugate vaccine compared with polysaccharide vaccine in patients with Crohn's disease - one year follow up. *Infect Dis* 2019;**51**:651–8.
315. Melmed GY, Agarwal N, Frenck RW, *et al*. Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010;**105**:148–54.
316. Fiorino G, Peyrin-Biroulet L, Naccarato P, *et al*. Effects of immunosuppression on immune response to pneumococcal vaccine in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis* 2012;**18**:1042–7.
317. Brodmerkel C, Wadman E, Langley RG, *et al*. Immune response to pneumococcus and tetanus toxoid in patients with moderate-to-severe psoriasis following long-term ustekinumab use. *J Drugs Dermatol* 2013;**12**:1122–9.
318. Kantsø B, Halkjær SI, Thomsen OØ, *et al*. Immunosuppressive drugs impairs antibody response of the polysaccharide and conjugated pneumococcal vaccines in patients with Crohn's disease. *Vaccine* 2015;**33**:5464–9.
319. Pittet LF, Verolet CM, Michetti P, *et al*.; Swiss Inflammatory Bowel Disease Cohort Study Group. High immunogenicity of the pneumococcal

conjugated vaccine in immunocompromised adults with inflammatory bowel disease. *Am J Gastroenterol* 2019;**114**:1130–41.
320. Centers for Disease Control and Prevention. *Legionnaires Disease Diagnosis, Treatment*. 2020. https://www.cdc.gov/legionella/clinicians/diagnostic-testing.html Accessed March 11, 2020.
321. Avni T, Bieber A, Green H, Steinmetz T, Leibovici L, Paul M. Diagnostic accuracy of PCR alone and compared with urinary antigen testing for detection of Legionella spp.: a systematic review. *J Clin Microbiol* 2016;**54**:401–11.
322. Htwe TH, Khardori NM. Legionnaire's disease and immunosuppressive drugs. *Infect Dis Clin North Am* 2017;**31**:29–42.
323. Lanternier F, Tubach F, Ravaud P, *et al*.; Research Axed on Tolerance of Biotherapies Group. Incidence and risk factors of Legionella pneumophila pneumonia during anti-tumor necrosis factor therapy: a prospective French study. *Chest* 2013;**144**:990–8.
324. Bodro M, Carratalà J, Paterson DL. Legionellosis and biologic therapies. *Respir Med* 2014;**108**:1223–8.
325. Fernández Llamas T, Sánchez Torres A, Egea Valenzuela J. Community-acquired pneumonia by Legionella pneumophila. Do we need to include new recommendations for inflammatory bowel disease patients under immunomodulators? *Rev Esp Enferm Dig* 2016;**108**:524.
326. Borrás-Blasco J, Cortes X, Fernandez-Martinez S, Casterá E, Antequera B. Legionella pneumophila pneumonia possibly due to ustekinumab therapy in a patient with Crohn's disease. *Am J Health Syst Pharm* 2017;**74**:209–12.
327. Wallis RS, Broder M, Wong J, Lee A, Hoq L. Reactivation of latent granulomatous infections by infliximab. *Clin Infect Dis* 2005;**41[Suppl 3]**:S194–8.
328. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006;**54**:2368–76.
329. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004;**38**:1261–5.
330. Fu A, Bertouch JV, McNeil HP. Disseminated Salmonella typhimurium infection secondary to infliximab treatment. *Arthritis Rheum* 2004;**50**:3049.
331. Katsarolis I, Tsiodras S, Panagopoulos P, *et al*. Septic arthritis due to Salmonella enteritidis associated with infliximab use. *Scand J Infect Dis* 2005;**37**:304–5.
332. Makkuni D, Kent R, Watts R, Clunie G. Two cases of serious food-borne infection in patients treated with anti-TNF-alpha. Are we doing enough to reduce the risk? *Rheumatology* 2006;**45**:237–8.
333. Netea MG, Radstake T, Joosten LA, van der Meer JW, Barrera P, Kullberg BJ. Salmonella septicemia in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: association with decreased interferon-gamma production and Toll-like receptor 4 expression. *Arthritis Rheum* 2003;**48**:1853–7.
334. Rijkeboer A, Voskuyl A, Van Agtmael M. Fatal Salmonella enteritidis septicaemia in a rheumatoid arthritis patient treated with a TNF-alpha antagonist. *Scand J Infect Dis* 2007;**39**:80–3.
335. Eke UA, Conte H, Anderson P, Lyons RW. Invasive Salmonellosis by the very rare Salmonella choleraesuis in a returning traveler on a tumor necrosis factor-α inhibitor. *Case Rep Med* 2014;**2014**:934657.
336. Saddler K, Castro-Lainez MT, Deliz-Aguirre R, *et al*. Nontyphoidal Salmonella purulent pericarditis presenting with pericardial tamponade in a patient on infliximab therapy. *IDCases* 2019;**15**:e00500.
337. Steinebrunner N, Sandig C, Zimmermann S, Stremmel W, Eisenbach C, Mischnik A. Salmonella enterica serovar Minnesota urosepsis in a patient with Crohn's disease in the absence of recent or current gastrointestinal symptoms. *J Med Microbiol* 2013;**62**:1360–2.
338. Gulan G, Jotanovic Z, Jurdana H, Sestan B, Ravlic-Gulan J, Brncic N. Salmonella typhimurium osteomyelitis of the femur in patient with Crohn's disease. *Wien Klin Wochenschr* 2010;**122**:437–40.
339. Sado AI, Kalla R, Sharma A. A case of IBD immunosuppression related salmonella aortitis requiring emergency vascular grafting. *Inflamm Bowel Dis* 2019;**25**:e64.
340. Rim JY, Tenorio AR. Salmonella septic arthritis in a patient with Crohn's disease on infliximab. *Inflamm Bowel Dis* 2010;**16**:545–7.
341. Mansour E, El-Masri F. Bilateral salmonella septic arthritis of the hip in a patient with Crohn disease: a case report. *JBJS Case Connect* 2016;**6**:e91.
342. Bodey GP, Fainstein V. Infections of the gastrointestinal tract in the immunocompromised patient. *Annu Rev Med* 1986;**37**:271–81.
343. Shivaji UN, Sharratt CL, Thomas T, *et al*. Review article: managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2019;**49**:664–80.
344. Quezada SM, McLean LP, Cross RK. Adverse events in IBD therapy: the 2018 update. *Expert Rev Gastroenterol Hepatol* 2018;**12**:1183–91.
345. Ng SC, Chan FK. Infections and inflammatory bowel disease: challenges in Asia. *J Dig Dis* 2013;**14**:567–73.
346. Wing EJ, Gregory SH. Listeria monocytogenes: clinical and experimental update. *J Infect Dis* 2002;**185[Suppl 1**:S18–24.
347. Abreu C, Magro F, Vilas-Boas F, Lopes S, Macedo G, Sarmento A. Listeria infection in patients on anti-TNF treatment: report of two cases and review of the literature. *J Crohns Colitis* 2013;**7**:175–82.
348. Chuang MH, Singh J, Ashouri N, Katz MH, Arrieta AC. Listeria meningitis after infliximab treatment of ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2010;**50**:337–9.
349. Gil C, Legido J, Cuenca C, *et al*. [Meningitis due to Listeria monocytogenes during adalimumab therapy]. *Gastroenterol Hepatol* 2009;**32**:587–8.
350. Murphy G, Schmidt-Martin D, Hynes BG, Harney S. Systemic listeriosis with adalimumab therapy. *J Clin Rheumatol* 2009;**15**:369–70.
351. Peña-Sagredo JL, Hernández MV, Fernandez-Llanio N, *et al*.; Biobadaser group. Listeria monocytogenes infection in patients with rheumatic diseases on TNF-alpha antagonist therapy: the Spanish Study Group experience. *Clin Exp Rheumatol* 2008;**26**:854–9.
352. Ramos JM, García-Sepulcre MF, Masiá M, Brotons A, Grau MC, Gutiérrez F. Listeria monocytogenes infection in patients with inflammatory bowel diseases receiving anti-tumor necrosis factor therapy. *Rev Esp Enferm Dig* 2010;**102**:614–6.
353. Slifman NR, Gershon SK, Lee JH, Edwards ET, Braun MM. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. *Arthritis Rheum* 2003;**48**:319–24.
354. Atsawarungruangkit A, Dominguez F, Borda G, Mavrogiorgos N. Listeria monocytogenes brain abscess in Crohn's disease treated with adalimumab. *Case Rep Gastroenterol* 2017;**11**:667–71.
355. Horigome R, Sato H, Honma T, Terai S. Septicemic listeriosis during adalimumab- and golimumab-based treatment for ulcerative colitis: case presentation and literature review. *Clin J Gastroenterol* 2020;**13**:22–5.
356. Miranda-Bautista J, Padilla-Suárez C, Bouza E, Muñoz P, Menchén L, Marín-Jiménez I. Listeria monocytogenes infection in inflammatory bowel disease patients: case series and review of the literature. *Eur J Gastroenterol Hepatol* 2014;**26**:1247–52.
357. Nanau RM, Cohen LE, Neuman MG. Risk of infections of biological therapies with accent on inflammatory bowel disease. *J Pharm Pharm Sci* 2014;**17**:485–531.
358. Parihar V, Maguire S, Shahin A, *et al*. Listeria meningitis complicating a patient with ulcerative colitis on concomitant infliximab and hydrocortisone. *Ir J Med Sci* 2016;**185**:965–7.
359. Stratton L, Caddy GR. Listeria rhombencephalitis complicating anti-TNF treatment during an acute flare of Crohn's colitis. *Case Rep Gastrointest Med* 2016;**2016**:6216128.
360. Tsuchiya A, Terai S. Listeria meningitis during infliximab-based treatment for ulcerative colitis. *Intern Med* 2018;**57**:2603.
361. Żak-Gołąb A, Dąbrowski K, Hrycek A. [Listeriosis of central nervous system in patients with ulcerative colitis - case study]. *Wiad Lek* 2017;**70**:685–8.
362. Furuya-Kanamori L, Stone JC, Clark J, *et al*. Comorbidities, exposure to medications, and the risk of community-acquired Clostridium difficile infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol* 2015;**36**:132–41.

363. Martinelli M, Strisciuglio C, Veres G, *et al*.; Porto IBD Working Group of European Society for Pediatric Gastroenterology, Hepatology and Nutrition [ESPGHAN]. Clostridium difficile and pediatric inflammatory bowel disease: a prospective, comparative, multicenter, ESPGHAN study. *Inflamm Bowel Dis* 2014;**20**:2219–25.
364. Singh H, Nugent Z, Yu BN, Lix LM, Targownik LE, Bernstein CN. Higher incidence of Clostridium difficile infection among individuals with inflammatory bowel disease. *Gastroenterology* 2017;**153**:430–8.e2.
365. Balram B, Battat R, Al-Khoury A, *et al*. Risk factors associated with Clostridium difficile infection in inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis* 2019;**13**:27–38.
366. Sokol H, Lalande V, Landman C, *et al*. Clostridium difficile infection in acute flares of inflammatory bowel disease: a prospective study. *Dig Liver Dis* 2017;**49**:643–6.
367. Garcia PG, Chebli LA, da Rocha Ribeiro TC, *et al*. Impact of superimposed Clostridium difficile infection in Crohn's or ulcerative colitis flares in the outpatient setting. *Int J Colorectal Dis* 2018;**33**:1285–94.
368. Chen XL, Deng J, Chen X, Wan SS, Wang Y, Cao Q. High incidence and morbidity of Clostridium difficile infection among hospitalized patients with inflammatory bowel disease: a prospective observational cohort study. *J Dig Dis* 2019;**20**:460–6.
369. Anderson A, Click B, Ramos-Rivers C, *et al*. Lasting impact of Clostridium difficile infection in inflammatory bowel disease: a propensity score matched analysis. *Inflamm Bowel Dis* 2017;**23**:2180–8.
370. Pant C, Anderson MP, Deshpande A, *et al*. Health care burden of Clostridium difficile infection in hospitalized children with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;**19**:1080–5.
371. Rao K, Malani PN. Diagnosis and treatment of Clostridioides [Clostridium] difficile infection in adults in 2020. *JAMA* 2020;**323**:1403–4.
372. Pollock NR, Banz A, Chen X, *et al*. Comparison of Clostridioides difficile stool toxin concentrations in adults with symptomatic infection and asymptomatic carriage using an ultrasensitive quantitative immunoassay. *Clin Infect Dis* 2019;**68**:78–86.
373. Kufelnicka AM, Kirn TJ. Effective utilization of evolving methods for the laboratory diagnosis of Clostridium difficile infection. *Clin Infect Dis* 2011;**52**:1451–7.
374. Wong KK, Choi B, Fraser TG, Donskey CJ, Deshpande A. Diagnostic testing methods for Clostridium difficile infection: a statewide survey of Ohio acute care hospitals. *Am J Infect Control* 2017;**45**:306–7.
375. Crobach MJ, Planche T, Eckert C, *et al*. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for Clostridium difficile infection. *Clin Microbiol Infect* 2016;**22[Suppl 4]**:S63–81.
376. Cohen SH, Gerding DN, Johnson S, *et al*.; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America [SHEA] and the Infectious Diseases Society of America [IDSA]. *Infect Control Hosp Epidemiol* 2010;**31**:431–55.
377. Planche T, Aghaizu A, Holliman R, *et al*. Diagnosis of Clostridium difficile infection by toxin detection kits: a systematic review. *Lancet Infect Dis* 2008;**8**:777–84.
378. Longtin Y, Trottier S, Brochu G, *et al*. Impact of the type of diagnostic assay on Clostridium difficile infection and complication rates in a mandatory reporting program. *Clin Infect Dis* 2013;**56**:67–73.
379. van den Berg RJ, Vaessen N, Endtz HP, Schülin T, van der Vorm ER, Kuijper EJ. Evaluation of real-time PCR and conventional diagnostic methods for the detection of Clostridium difficile-associated diarrhoea in a prospective multicentre study. *J Med Microbiol* 2007;**56**:36–42.
380. Bartlett JG. Narrative review: the new epidemic of Clostridium difficile-associated enteric disease. *Ann Intern Med* 2006;**145**:758–64.
381. Reigadas E, Alcalá L, Marín M, Martín A, Iglesias C, Bouza E. Role of binary toxin in the outcome of Clostridium difficile infection in a non-027 ribotype setting: CORRIGENDUM. *Epidemiol Infect* 2016;**144**:2691.
382. Gupta A, Wash C, Wu Y, *et al*. Diagnostic modality of Clostridioides difficile infection predicts treatment response and outcomes in inflammatory bowel disease. *Dig Dis Sci* 2021;**66**:547–53.
383. Elliott B, Chang BJ, Golledge CL, Riley TV. Clostridium difficile-associated diarrhoea. *Intern Med J* 2007;**37**:561–8.
384. Ben-Horin S, Margalit M, Bossuyt P, *et al*.; European Crohn's and Colitis Organisation [ECCO]. Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and Clostridium difficile infection. *J Crohns Colitis* 2010;**4**:194–8.
385. Johnson S, Louie TJ, Gerding DN, *et al*.; Polymer Alternative for CDI Treatment [PACT] investigators. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis* 2014;**59**:345–54.
386. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis* 2007;**45**:302–7.
387. Louie TJ, Miller MA, Mullane KM, *et al*.; OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for Clostridium difficile infection. *N Engl J Med* 2011;**364**:422–31.
388. Cornely OA, Crook DW, Esposito R, *et al*.; OPT-80-004 Clinical Study Group. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomized controlled trial. *Lancet Infect Dis* 2012;**12**:281–9.
389. McDonald LC, Gerding DN, Johnson S, *et al*. Clinical Practice Guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America [IDSA] and Society for Healthcare Epidemiology of America [SHEA]. *Clin Infect Dis* 2018;**66**:987–94.
390. Cornely OA, Miller MA, Louie TJ, Crook DW, Gorbach SL. Treatment of first recurrence of Clostridium difficile infection: fidaxomicin versus vancomycin. *Clin Infect Dis* 2012;**55[Suppl 2]**:S154–61.
391. Debast SB, Bauer MP, Kuijper EJ; European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. *Clin Microbiol Infect* 2014;**20[Suppl 2]**:1–26.
392. Tariq R, Pardi DS, Bartlett MG, Khanna S. Low cure rates in controlled trials of fecal microbiota transplantation for recurrent Clostridium difficile infection: a systematic review and meta-analysis. *Clin Infect Dis* 2019;**68**:1351–8.
393. Chen T, Zhou Q, Zhang D, *et al*. Effect of faecal microbiota transplantation for treatment of Clostridium difficile infection in patients with inflammatory bowel disease: a systematic review and meta-analysis of cohort studies. *J Crohns Colitis* 2018;**12**:710–7.
394. Lan N, Ashburn J, Shen B. Fecal microbiota transplantation for Clostridium difficile infection in patients with ileal pouches. *Gastroenterol Rep* 2017;**5**:200–7.
395. Goldenberg JZ, Yap C, Lytvyn L, *et al*. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. *Cochrane Database Syst Rev* 2017;**12**:CD006095.
396. Wilcox MH, Gerding DN, Poxton IR, *et al*.; MODIFY I and MODIFY II Investigators. Bezlotoxumab for prevention of recurrent Clostridium difficile infection. *N Engl J Med* 2017;**376**:305–17.
397. Issa M, Vijayapal A, Graham MB, *et al*. Impact of Clostridium difficile on inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007;**5**:345–51.
398. Leca M, Bornet C, Montana M, Curti C, Vanelle P. Meningococcal vaccines: current state and future outlook. *Pathol Biol* 2015;**63**:144–51.
399. Mbaeyi SA, Bozio CH, Duffy J, *et al*. Meningococcal vaccination: recommendations of the advisory committee on immunization practices, United States, 2020. *MMWR Recomm Rep* 2020;**69**:1–41.
400. Public Health Agency of Canada. *Canadian Immunization Guide*. Ottawa: PHAC; 2015.
401. European Center for Disease Prevention and Control [ECDC]. *Meningococcal Disease: Recommended Vaccinations*. Solna, Sweden: ECDC; 2020.
402. Di Sabatino A, Rosado MM, Ciccocioppo R, *et al*. Depletion of immunoglobulin M memory B cells is associated with splenic hypofunction in inflammatory bowel disease. *Am J Gastroenterol* 2005;**100**:1788–95.
403. Ryan FP, Smart R, Preston FE, Holdsworth CD. Hyposplenism in ulcerative colitis. *Lancet* 1974;**2**:318–20.

404. Ardeman S, Bevan G, Smith W. Hyposplenism and ulcerative colitis. *Lancet* 1974;**304**:588.
405. Ryan FP, Smart RC, Holdsworth CD, Preston FE. Hyposplenism in inflammatory bowel disease. *Gut* 1978;**19**:50–5.
406. Palmer KR, Sherriff SB, Holdsworth CD, Ryan FP. Further experience of hyposplenism in inflammatory bowel disease. *Q J Med* 1981;**50**:463–71.
407. Majumder S, Kumar A. Meningococcal meningoencephalitis after certolizumab pegol treatment in a patient with Crohn's disease. *J Crohns Colitis* 2013;**7**:e19.
408. Salinas N, Etienne M, Roguedas AM, *et al*. Méningococcémie subaiguë sous adalimumab (Subacute meningococcaemia during adalimumab therapy). *Ann Dermatol Venereol* 2019;**146**:817–20.
409. Kochar B, Jiang Y, Long MD. Patients with inflammatory bowel diseases are at higher risk for meningitis. *J Clin Gastroenterol* 2021;**55**:350–4.
410. Keene JK, Lowe DK, Grosfeld JL, Fitzgerald JF, Gonzales-Crussi F. Disseminated varicella complicating ulcerative colitis. *JAMA* 1978;**239**:45–6.
411. Gurvits GE, Lan G, Tan A, Weissman A. Vaccination practices in patients with inflammatory bowel disease among general internal medicine physicians in the USA. *Postgrad Med J* 2017;**93**:333–7.
412. Jung YS, Park JH, Kim HJ, *et al*. Insufficient knowledge of Korean gastroenterologists regarding the vaccination of patients with inflammatory bowel disease. *Gut Liver* 2014;**8**:242–7.
413. Furer V, Rondaan C, Heijstek MW, *et al*. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020;**79**:39–52.
414. Rubin LG, Levin MJ, Ljungman P, *et al*. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014;**58**:309–18.
415. Zhang J, Delzell E, Xie F, *et al*. The use, safety, and effectiveness of herpes zoster vaccination in individuals with inflammatory and autoimmune diseases: a longitudinal observational study. *Arthritis Res Ther* 2011;**13**:R174.
416. Zhang J, Xie F, Delzell E, *et al*. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA* 2012;**308**:43–9.
417. Lu Y, Bousvaros A. Varicella vaccination in children with inflammatory bowel disease receiving immunosuppressive therapy. *J Pediatr Gastroenterol Nutr* 2010;**50**:562–5.
418. Ekenberg C, Moller NF, Ulstrup T, *et al*. Inadvertent yellow fever vaccination of a patient with Crohn's disease treated with infliximab and methotrexate. *BMJ Case Rep* 2016;**2016**.
419. Nash ER, Brand M, Chalkias S. Yellow fever vaccination of a primary vaccinee during adalimumab therapy. *J Travel Med* 2015;**22**:279–81.
420. Rüddel J, Schleenvoigt BT, Schüler E, Schmidt C, Pletz MW, Stallmach A. Yellow fever vaccination during treatment with infliximab in a patient with ulcerative colitis: a case report. *Z Gastroenterol* 2016;**54**:1081–4.
421. Buhler S, Jaeger VK, Eperon G, *et al*. Safety and immunogenicity of a primary yellow fever vaccination under low-dose methotrexate therapy - a prospective multi-centre pilot study1. *J Travel Med* 2020;**27**:taaa126.
422. Wichmann A, Krugliak Cleveland N, Rubin DT. Safety and efficacy of live measles vaccine administered to a Crohn's disease patient receiving vedolizumab. *Am J Gastroenterol* 2016;**111**:577.
423. McLean HQ, Fiebelkorn A, Temte JL, *et al*. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR Recomm Rep* 2013;**62**:1–34.
424. Caldera F, Misch EA, Saha S, *et al*. Immunosuppression does not affect antibody concentrations to measles, mumps, and rubella in patients with inflammatory bowel disease. *Dig Dis Sci* 2019;**64**:189–95.
425. Croce E, Hatz C, Jonker EF, Visser LG, Jaeger VK, Bühler S. Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation - a systematic review of randomised trials, observational studies and case reports. *Vaccine* 2017;**35**:1216–26.
426. Waszczuk K, Waszczuk E, Mulak A, Szenborn L, Paradowski L. A 'cocoon immunization strategy' among patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2015;**27**:249–53.
427. *The Green Book: Immunisation Against Infectious Disease. Chapter 6: Contraindications and Special Considerations*. 2017:1–12.
428. *The Green Book: Immunisation Against Infectious Disease*. Public Health England; published 17 December 2013, last updated 21 January 2021.
429. H. *C.S. Vaccination of Immunocompromised or Chronically Ill Children and/or Adults*. SHC report 9158, 2019.
430. Sahasranaman S, Howard D, Roy S. Clinical pharmacology and pharmacogenetics of thiopurines. *Eur J Clin Pharmacol* 2008;**64**:753–67.
431. Chan GL, Erdmann GR, Gruber SA, Matas AJ, Canafax DM. Azathioprine metabolism: pharmacokinetics of 6-mercaptopurine, 6-thiouric acid and 6-thioguanine nucleotides in renal transplant patients. *J Clin Pharmacol* 1990;**30**:358–63.
432. Lexicomp. *Lexi Drugs Online*. 2020.online.lexi.com Accessed October 14, 2020.
433. Abreu C, Rocha-Pereira N, Sarmento A, Magro F. Nocardia infections among immunomodulated inflammatory bowel disease patients: a review. *World J Gastroenterol* 2015;**21**:6491–8.
434. Garner O, Ramirez-Berlioz A, Iardino A, Mocherla S, Bhairavarasu K. Disseminated nocardiosis associated with treatment with infliximab in a patient with ulcerative colitis. *Am J Case Rep* 2017;**18**:1365–9.
435. Verstockt B, Van Hemelen M, Outtier A, *et al*. Invasive nocardiosis, disseminated varicella zoster reactivation, and pneumocystis jiroveci pneumonia associated with tofacitinib and concomitant systemic corticosteroid use in ulcerative colitis. *J Gastroenterol Hepatol* 2020;**35**:2294–7.
436. Mandell LA, Wunderink RG, Anzueto A, *et al*.; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;**44[Suppl 2]**:S27–72.
437. Fabre S, Gibert C, Lechiche C, Jorgensen C, Sany J. Primary cutaneous Nocardia otitidiscaviarum infection in a patient with rheumatoid arthritis treated with infliximab. *J Rheumatol* 2005;**32**:2432–3.
438. Singh SM, Rau NV, Cohen LB, Harris H. Cutaneous nocardiosis complicating management of Crohn's disease with infliximab and prednisone. *CMAJ* 2004;**171**:1063–4.
439. Verstockt B, Vermeire S, Van Assche G, Ferrante M. When IBD is not IBD. *Scand J Gastroenterol* 2018;**53**:1085–8.
440. Gecse KB, Vermeire S. Differential diagnosis of inflammatory bowel disease: imitations and complications. *Lancet Gastroenterol Hepatol* 2018;**3**:644–53.
441. Loutfy MR, Wilson M, Keystone JS, Kain KC. Serology and eosinophil count in the diagnosis and management of strongyloidiasis in a non-endemic area. *Am J Trop Med Hyg* 2002;**66**:749–52.
442. Long MD, Farraye FA, Okafor PN, Martin C, Sandler RS, Kappelman MD. Increased risk of pneumocystis jiroveci pneumonia among patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;**19**:1018–24.
443. Nam K, Park SH, Lee J, *et al*. Incidence and risk factors of Pneumocystis jirovecii pneumonia in Korean patients with inflammatory bowel disease. *J Gastroenterol Hepatol* 2020;**35**:218–24.
444. Lawrence SJ, Sadarangani M, Jacobson K. Pneumocystis jirovecii pneumonia in pediatric inflammatory bowel disease: a case report and literature review. *Front Pediatr* 2017;**5**:161.
445. Okafor PN, Farraye FA, Okafor AT, Erim DO. Cost-effectiveness of prophylaxis against Pneumocystis jiroveci pneumonia in patients with Crohn's disease. *Dig Dis Sci* 2015;**60**:3743–55.
446. Macaluso FS, Cottone M, Orlando A. Risk of pneumonia caused by Pneumocystis jiroveci in inflammatory bowel disease: the role of concomitant pulmonary comorbidities. *Clin Gastroenterol Hepatol* 2019;**17**:571–2.
447. Cotter TG, Gathaiya N, Catania J, *et al*. Low risk of pneumonia from Pneumocystis jirovecii infection in patients with inflammatory bowel

disease receiving immune suppression. *Clin Gastroenterol Hepatol* 2017;**15**:850–6.
448. Okafor PN, Nunes DP, Farraye FA. Pneumocystis jiroveci pneumonia in inflammatory bowel disease: when should prophylaxis be considered? *Inflamm Bowel Dis* 2013;**19**:1764–71.
449. Sandborn WJ, Rutgeerts P, Gasink C, *et al*. Long-term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy. *Aliment Pharmacol Ther* 2018;**48**:65–77.
450. Reinwald M, Silva JT, Mueller NJ, *et al*. ESCMID Study Group for Infections in Compromised Hosts [ESGICH] Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective [intracellular signaling pathways: tyrosine kinase and mTOR inhibitors]. *Clin Microbiol Infect* 2018;**24**[**Suppl 2**]:53–70.
451. Preston C. *Stockley's Drug Interactions*. 12th edn. London: Pharmaceutical Press; 2019.
452. Avino LJ, Naylor SM, Roecker AM. Pneumocystis jirovecii pneumonia in the non-HIV-infected population. *Ann Pharmacother* 2016;**50**:673–9.
453. Jaeger VK, Rüegg R, Steffen R, Hatz C, Bühler S. Travelers with immune-mediated inflammatory diseases: are they different? *J Travel Med* 2015;**22**:161–7.
454. Philip V, Soubieres A, Poullis A. Health concerns associated with travelling with inflammatory bowel disease [IBD]: a questionnaire survey. *Clin Med* 2018;**18**:288–92.
455. Chan W, Shim HH, Ng SC, *et al*.; Asia–Pacific Crohn's and Colitis Epidemiologic Study [ACCESS] Study Group. A global survey of gastroenterologists' travel advice to patients with inflammatory bowel disease on immunosuppressive agents, and management of those visiting tuberculosis-endemic areas. *J Crohns Colitis* 2018;**12**:1261–9.
456. Greveson K, Shepherd T, Mulligan JP, *et al*. Travel health and pretravel preparation in the patient with inflammatory bowel disease. *Frontline Gastroenterol* 2016;**7**:60–5.
457. Tan EM, Marcelin JR, Virk A. Pre-travel counseling for immunocompromised travelers: a 12-year single-center retrospective review. *Infect Dis Health* 2019;**24**:13–22.
458. Ellul P, Fenech VA, Azzopardi C, *et al*. Diarrhoeal episodes in travellers suffering from IBD. *Frontline Gastroenterol* 2013;**4**:120–4.
459. Baaten GG, Geskus RB, Kint JA, Roukens AH, Sonder GJ, van den Hoek A. Symptoms of infectious diseases in immunocompromised travelers: a prospective study with matched controls. *J Travel Med* 2011;**18**:318–26.
460. Ben-Horin S, Bujanover Y, Goldstein S, *et al*. Travel-associated health risks for patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2012;**10**:160–5, 165.e1.
461. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2013;**108**:1268–76.
462. Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor alpha blockade therapy. *Mayo Clin Proc* 2008;**83**:181–94.
463. Poeppl W, Oeser C, Grabmeier-Pfistershammer K, Walochnik J, Burgmann H. Clinical findings and management of imported cutaneous leishmaniasis: report of 14 cases from Austria. *Travel Med Infect Dis* 2013;**11**:90–4.
464. Hofland RW, Thijsen SF, Verhagen MA, Schenk Y, Bossink AW. Tuberculosis during TNF-α inhibitor therapy, despite screening. *Thorax* 2013;**68**:1079–80.
465. Schwartz T, Jensenius M, Blomberg B, Fladeby C, Mæland A, Pettersen FO. Imported visceral leishmaniasis and immunosuppression in seven Norwegian patients. *Trop Dis Travel Med Vaccines* 2019;**5**:16.
466. Gaut D, Shull H, Bejjani A, Kahn D. Hepatic abscess in a returning traveler with Crohn's disease: differentiating amebic from pyogenic liver abscess. *Case Rep Med* 2018;**2018**:9593865.
467. Lucey O, Carroll I, Bjorn T, Millar M. Reactivation of latent Histoplasma and disseminated cytomegalovirus in a returning traveller with ulcerative colitis. *JMM Case Rep* 2018;**5**:e005170.
468. Roure S, Valerio L, Soldevila L, *et al*. Approach to amoebic colitis: epidemiological, clinical and diagnostic considerations in a non-endemic context [Barcelona, 2007-2017]. *PLoS One* 2019;**14**:e0212791.
469. Marcoval J, Penín RM. Evolution of cutaneous leishmaniasis in the last 30 years in a tertiary hospital of the European Mediterranean coast. *Int J Dermatol* 2017;**56**:750–3.
470. World Health Organization. *International Travel and Health*. Geneva: WHO; 2012.
471. Stallmach A, Carstens O. Role of infections in the manifestation or reactivation of inflammatory bowel diseases. *Inflamm Bowel Dis* 2002;**8**:213–8.
472. Powell SJ, Wilmot AJ. Ulcerative post-dysenteric colitis. *Gut* 1966;**7**:438–43.
473. Treacher DF, Jewell DP. Yersinia colitis associated with Crohn's disease. *Postgrad Med J* 1985;**61**:173–4.
474. Axelrad JE, Joelson A, Green PHR, *et al*. Enteric infections are common in patients with flares of inflammatory bowel disease. *Am J Gastroenterol* 2018;**113**:1530–9.
475. Soonawala D, van Eggermond AM, Fidder H, Visser LG. Pretravel preparation and travel-related morbidity in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**18**:2079–85.
476. Feagins LA, Iqbal R, Spechler SJ. Case-control study of factors that trigger inflammatory bowel disease flares. *World J Gastroenterol* 2014;**20**:4329–34.
477. Vavricka SR, Rogler G, Maetzler S, *et al*. High altitude journeys and flights are associated with an increased risk of flares in inflammatory bowel disease patients. *J Crohns Colitis* 2014;**8**:191–9.
478. Fruehauf H, Vavricka SR, Lutz TA, *et al*. Evaluation of acute mountain sickness by unsedated transnasal esophagogastroduodenoscopy at high altitude. *Clin Gastroenterol Hepatol* 2020;**18**:2218–25.e2.
479. Geraghty EM, Ristow B, Gordon SM, Aronowitz P. Overwhelming parasitemia with Plasmodium falciparum infection in a patient receiving infliximab therapy for rheumatoid arthritis. *Clin Infect Dis* 2007;**44**:e82–4.
480. Wassmer SC, Cianciolo GJ, Combes V, Grau GE. Inhibition of endothelial activation: a new way to treat cerebral malaria? *PLoS Med* 2005;**2**:e245.
481. Lewis J, Gregorian T, Portillo I, *et al*. Drug interactions with antimalarial medications in older travelers: a clinical guide. *J Travel Med* 2020;**27**:taz089.
482. Jia K, Tong X, Wang R, Song X. The clinical effects of probiotics for inflammatory bowel disease: a meta-analysis. *Medicine* 2018;**97**:e13792.
483. Dang X, Xu M, Liu D, Zhou D, Yang W. Assessing the efficacy and safety of fecal microbiota transplantation and probiotic VSL#3 for active ulcerative colitis: a systematic review and meta-analysis. *PLoS One* 2020;**15**:e0228846.
484. Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomized trial. *Lancet* 1999;**354**:635–9.
485. Kruis W, Fric P, Pokrotnieks J, *et al*. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. *Gut* 2004;**53**:1617–23.
486. Borriello SP, Hammes WP, Holzapfel W, *et al*. Safety of probiotics that contain lactobacilli or bifidobacteria. *Clin Infect Dis* 2003;**36**:775–80.
487. Saxelin M, Chuang NH, Chassy B, *et al*. Lactobacilli and bacteremia in southern Finland, 1989-1992. *Clin Infect Dis* 1996;**22**:564–6.
488. Thygesen JB, Glerup H, Tarp B. Saccharomyces boulardii fungemia caused by treatment with a probioticum. *BMJ Case Rep* 2012;**2012**:bcr0620114412.
489. Cunningham-Rundles S, Ahrné S, Bengmark S, *et al*. Probiotics and immune response. *Am J Gastroenterol* 2000;**95**:S22–5.
490. Wolf BW, Wheeler KB, Ataya DG, Garleb KA. Safety and tolerance of Lactobacillus reuteri supplementation to a population infected with the human immunodeficiency virus. *Food Chem Toxicol* 1998;**36**:1085–94.
491. Elsner HA, Sobottka I, Mack D, Claussen M, Laufs R, Wirth R. Virulence factors of Enterococcus faecalis and Enterococcus faecium blood culture isolates. *Eur J Clin Microbiol Infect Dis* 2000;**19**:39–42.
492. Kothari D, Patel S, Kim SK. Probiotic supplements might not be universally-effective and safe: a review. *Biomed Pharmacother* 2019;**111**:537–47.
493. Huycke MM, Spiegel CA, Gilmore MS. Bacteremia caused by hemolytic, high-level gentamicin-resistant Enterococcus faecalis. *Antimicrob Agents Chemother* 1991;**35**:1626–34.

494. Kanis SL, de Lima-Karagiannis A, van der Ent C, Rizopoulos D, van der Woude CJ. Anti-TNF levels in cord blood at birth are associated with anti-TNF type. *J Crohns Colitis* 2018;**12**:939–47.
495. Mahadevan U, Wolf DC, Dubinsky M, *et al*. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013;**11**:286–92; quiz e24.
496. Zelinkova Z, van der Ent C, Bruin KF, *et al*.; Dutch Delta IBD Group. Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. *Clin Gastroenterol Hepatol* 2013;**11**:318–21.
497. de Lima A, Zelinkova Z, van der Ent C, Steegers EA, van der Woude CJ. Tailored anti-TNF therapy during pregnancy in patients with IBD: maternal and fetal safety. *Gut* 2016;**65**:1261–8.
498. Julsgaard M, Christensen LA, Gibson PR, *et al*. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 2016;**151**:110–9.
499. Labetoulle R, Roblin X, Paul S. Prolonged persistence of adalimumab transferred from mother to infant during pregnancy. *Ann Intern Med* 2018;**169**:60–1.
500. Duricova D, Dvorakova E, Hradsky O, *et al*. Safety of anti-TNF-alpha therapy during pregnancy on long-term outcome of exposed children: a controlled, multicenter observation. *Inflamm Bowel Dis* 2019;**25**:789–96.
501. Chaparro M, Verreth A, Lobaton T, *et al*. Long-term safety of in utero exposure to anti-TNFα drugs for the treatment of inflammatory bowel disease: results from the multicenter European TEDDY study. *Am J Gastroenterol* 2018;**113**:396–403.
502. Luu M, Benzenine E, Doret M, *et al*. Continuous anti-TNFα use throughout pregnancy: possible complications for the mother but not for the fetus. a Retrospective Cohort on the French National Health Insurance Database [EVASION]. *Am J Gastroenterol* 2018;**113**:1669–77.
503. Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. *Am J Gastroenterol* 2013;**108**:1426–38.
504. Beaulieu DB, Ananthakrishnan AN, Martin C, Cohen RD, Kane SV, Mahadevan U. Use of biologic therapy by pregnant women with inflammatory bowel disease does not affect infant response to vaccines. *Clin Gastroenterol Hepatol* 2018;**16**:99–105.
505. de Lima A, Kanis SL, Escher JC, van der Woude CJ. Hepatitis B vaccination effective in children exposed to anti-tumour necrosis factor alpha in utero. *J Crohns Colitis* 2018;**12**:948–53.
506. Sheibani S, Cohen R, Kane S, Dubinsky M, Church JA, Mahadevan U. The effect of maternal peripartum anti-TNFα use on infant immune response. *Dig Dis Sci* 2016;**61**:1622–7.
507. Esteve-Solé A, Deyà-Martínez À, Teixidó I, *et al*. Immunological changes in blood of newborns exposed to anti-TNF-α during pregnancy. *Front Immunol* 2017;**8**:1123.
508. Vestergaard T, Kammerlander H, Brock B, Julsgaard M. Immunoglobulin and infliximab concentrations in dichorionic twins exposed to infliximab in utero. *J Crohns Colitis* 2017;**11**:1152–3.
509. Bortlik M, Duricova D, Machkova N, *et al*. Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. *Inflamm Bowel Dis* 2014;**20**:495–501.
510. Luu M, Benzenine E, Barkun A, *et al*. Safety of first year vaccination in children born to mothers with inflammatory bowel disease and exposed in utero to anti-TNFα agents: a French nationwide population-based cohort. *Aliment Pharmacol Ther* 2019;**50**:1181–8.
511. Cheent K, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J Crohns Colitis* 2010;**4**:603–5.
512. van der Woude CJ, Ardizzone S, Bengtson MB, *et al*.; European Crohn's and Colitis Organisation. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. *J Crohns Colitis* 2015;**9**:107–24.
513. Vesikari T, Matson DO, Dennehy P, *et al*.; Rotavirus Efficacy and Safety Trial [REST] Study Team. Safety and efficacy of a pentavalent human-bovine [WC3] reassortant rotavirus vaccine. *N Engl J Med* 2006;**354**:23–33.
514. Berkhout A, Clark JE, Wen SC. In utero exposure to biologic disease-modifying anti-rheumatic drugs and effects to the infant: infectious complications, vaccine response, and safety of live vaccine administration. *Expert Rev Vaccines* 2019;**18**:495–504.
515. Lee KE, Jung SA, Park SH, *et al*. Influence of anti-tumor necrosis factor-alpha therapy to pregnant inflammatory bowel disease women and their children's immunity. *Intest Res* 2019;**17**:237–43.
516. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS; Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR Recomm Rep* 2013;**62**:1–34.
517. van der Woude CJ, Kanis SL. IBD: exposure to anti-TNF agents in utero: controlling health risks. *Nat Rev Gastroenterol Hepatol* 2016;**13**:387–8.
518. Cimaz R, Meregalli E, Biggioggero M, *et al*. Alterations in the immune system of children from mothers treated with immunosuppressive agents during pregnancy. *Toxicol Lett* 2004;**149**:155–62.
519. Biggioggero M, Borghi MO, Gerosa M, Trespidi L, Cimaz R, Meroni PI. Immune function in children born to mothers with autoimmune diseases and exposed in utero to immunosuppressants. *Lupus* 2007;**16**:651–6.
520. de Meij TG, Jharap B, Kneepkens CM, van Bodegraven AA, de Boer NK; Dutch Initiative on Crohn and Colitis. Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;**38**:38–43.
521. Dinelli MIS, Ono E, Viana PO, *et al*. Response to immunization in children born to renal transplant recipients using immunosuppressive drugs during gestation. *Vaccine* 2016;**34**:404–7.
522. Bar-Gil Shitrit A, Ben Ya'acov A, Livovsky DM, *et al*. Exposure to vedolizumab in IBD pregnant women appears of low risk for mother and neonate: a first prospective comparison study. *Am J Gastroenterol* 2019;**114**:1172–5.
523. Julsgaard M, Kjeldsen J, Brock B, Baumgart DC. Letter: vedolizumab drug levels in cord and maternal blood in women with inflammatory bowel disease. *Aliment Pharmacol Ther* 2018;**48**:386–8.
524. Rowan CR, Cullen G, Mulcahy HE, *et al*. Ustekinumab drug levels in maternal and cord blood in a woman with Crohn's disease treated until 33 weeks of gestation. *J Crohns Colitis* 2018;**12**:376–8.
525. Klenske E, Osaba L, Nagore D, Rath T, Neurath MF, Atreya R. Drug levels in the maternal serum, cord blood and breast milk of a ustekinumab-treated patient with Crohn's disease. *J Crohns Colitis* 2019;**13**:267–9.
526. Dinelli MIS, Dos Santos AMN, Weckx LY, de Moraes-Pinto MI. Safe administration of rotavirus vaccine in a cohort of infants exposed to immunosuppressive drugs during gestation. *Transpl Infect Dis* 2018;**20**:e12951.
527. Arsenescu R, Arsenescu V, de Villiers WJ. TNF-α and the development of the neonatal immune system: implications for inhibitor use in pregnancy. *Am J Gastroenterol* 2011;**106**:559–62.
528. Ben-Horin S, Yavzori M, Kopylov U, *et al*. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. *J Crohns Colitis* 2011;**5**:555–8.
529. Grosen A, Julsgaard M, Kelsen J, Christensen LA. Infliximab concentrations in the milk of nursing mothers with inflammatory bowel disease. *J Crohns Colitis* 2014;**8**:175–6.
530. Matro R, Martin CF, Wolf D, Shah SA, Mahadevan U. Exposure concentrations of infants breastfed by women receiving biologic therapies for inflammatory bowel diseases and effects of breastfeeding on infections and development. *Gastroenterology* 2018;**155**:696–704.
531. Gartner LM, Morton J, Lawrence RA, *et al*.; American Academy of Pediatrics Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics* 2005;**115**:496–506.
532. Carlson JA, Middleton PJ, Szymanski MT, Huber J, Petric M. Fatal rotavirus gastroenteritis: an analysis of 21 cases. *Am J Dis Child* 1978;**132**:477–9.
533. Gagnière C, Bourrier A, Seksik P, *et al*.; GETAID INFOPRO study group. Risk of serious infection in health care workers with inflammatory bowel disease: a case-control study of the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif [GETAID]. *Aliment Pharmacol Ther* 2018;**48**:713–22.