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REVIEW

Viral infections in inflammatory bowel disease: Tips and tricks for correct management

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Abstract

Over the past decades, the treatment of inflammatory bowel diseases (IBD) has become more targeted, anticipating the use of immune-modifying therapies at an earlier stage. This top-down approach has been correlated with favorable short and long-term outcomes, but it has also brought with it concerns regarding potential infectious complications. This large IBD population treated with immune-modifying therapies, especially if combined, has an increased risk of severe infections, including opportunistic infections that are sustained by viral, bacterial, parasitic, and fungal agents. Viral infections have emerged as a focal safety concern in patients with IBD, representing a challenge for the clinician: they are often difficult to diagnose and are associated with significant morbidity and mortality. The first step is to improve effective preventive strategies, such as applying vaccination protocols, adopt adequate prophylaxis and educate patients about potential risk factors. Since viral infections in immunosuppressed patients may present atypical signs and symptoms, the challenges for the gastroenterologist are to suspect, recognize and diagnose such complications. Appropriate treatment of common viral infections allows us to minimize their impact on disease outcomes and patients' lives. This practical review supports this standard of care to improve knowledge in this subject area.

Key Words: Inflammatory bowel diseases; Viral infections; Opportunistic infections; Standard of care; Crohn's disease; Ulcerative colitis

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Core Tip: The inflammatory bowel disease population treated with immune-modifying therapies is at increased risk of severe infections, including opportunistic infections sustained by viral agents. Of these opportunistic infections, 40% are due to viral pathogens, including hepatitis A virus, hepatitis C virus, hepatitis B virus, human papillomavirus, influenza virus, human immunodeficiency virus, herpes simplex virus, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, and severe acute respiratory syndrome coronavirus 2 (causing coronavirus disease 19). A challenge for the gastroenterologist is to adopt preventive measures, recognize and treat common viral infections to minimize their impact on disease outcomes and patients' lives. This practical review supports this standard of care, aiming to bridge the gap of knowledge in this subject area.

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INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC) are lifetime conditions characterized by a relapsing and remitting clinical course. The complete pathogenic mechanisms of IBD are unknown. The major hypothesis is that the diseases occur when genetically vulnerable individuals meet unknown environmental triggers that exacerbate an inappropriate immune response against gut microbiota[1]. Curative therapies for IBD are not available yet. Medical treatment aims to guarantee long-lasting disease remission, thus avoiding complications and improving patient quality of life.

Drugs currently available for the management of IBD are mesalazine (5-ASA), locally active steroids, systemic steroids, thiopurines such as azathioprine (AZA) and mercaptopurine (MP), methotrexate (MTX), and biological therapies [Tumor necrosis factor-alpha inhibitors (anti-TNF) and other monoclonal antibodies targeting interleukin 12 (IL-12), IL-23, and cellular adhesion molecule ligands a4 integrin and a4b7 integrin][2].

Over the past decades, IBD treatment has become more targeted, anticipating the use of immune-modifying therapies at an earlier stage[3,4]. This has been correlated with favorable prognosis such as a reduction in surgery, hospitalization, and use of steroids[5-10], but it has also brought with it concerns about potential infectious complications.

IBD patients treated with immune-modifying therapies have an increased risk of developing severe infections, including opportunistic infections sustained by viral, bacterial, parasitic, and fungal agents[11-16], that are associated with hospital admission, use of intravenous antimicrobials, disability and death. The incidence of serious infections is not well defined, ranging from 10 to 100 events per 1000 patient-years[13,17-19]. Opportunistic infections are caused by ordinarily nonpathogenic organisms that can take advantage of an impaired immune system. According to the European Crohn's and Colitis Organization (ECCO) consensus guidelines on the prevention, diagnosis and management of opportunistic infections in IBD[20], updated in 2014[12], IBD patients treated with immune-modifying agents, especially in combination, those with malnutrition, comorbidities and a history of severe infections should be considered at risk for opportunistic infections. In an era of intensifying immune-modifying therapies, infective complications have emerged as a focal safety concern in patients with IBD. Today's challenge for gastroenterologists is to adopt preventative strategies, suspect, recognize, and treat appropriately IBD infectious complications to minimize their impact on disease outcomes and patients' lives. In particular, viral infections represent demanding problems for the clinician, as they are often difficult to diagnose and are associated with significant morbidity. This review intends to outline the most relevant viral infections in IBD, focusing on the careful

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screening and monitoring before and during the use of immune-modifying therapies, timing of vaccinations, opportunity for primary or secondary prophylaxis and indications for therapy. A summary of recommendations for the prevention and management of viral infections in IBD are shown in Table 1.

VIRAL INFECTION IN IBD

Risk factors

A population-based study of patients with IBD[18] found that of opportunistic infections, 40% were due to viral pathogens. A recent prospective observational study [21] estimated that the incidence rate of systemic viral infections in patients with IBD was 2 per 1000 person-years, three-fold higher compared to the general population. Age is an independent risk factor for opportunistic infections in IBD[22], but for viral infections, the highest incidence rates are observed in patients under the age of 35 years[21]. In elderly patients, infections sustained by viral pathogens are rare compared with the younger population[23], except for influenza[24], herpes zoster reactivation (shingles)[25], and viral gastroenteritis[26]. Viral infections may also be triggered by disease activity and the resulting defective mucosal immunity, especially cytomegalovirus (CMV) colitis[27,28], and Epstein-Barr virus (EBV) systemic reactivation[29]. Finally, viral infections may arise as adverse events attributable to the immune-modifier action of IBD drugs. The direct correlation between a specific immunomodulator or biologic drug and viral infections has not been established. A retrospective analysis found that AZA/6MP-treated patients are at risk of developing opportunistic viral infections, such as herpes simplex (HSV), varicella-zoster (VZV), CMV, and EBV[11]. In a prospective cohort of outpatients with IBD, it was reported that exposure to thiopurines was associated with an increased incidence of cutaneous herpes flares and warts[30]. The incidence of zoster is increased in patients with IBD [31-33] and exposure to immunomodulators, in particular corticosteroids or combination therapy with thiopurines and anti-TNF agents, raises the risk[18,34]. During a 5-year follow-up, combination therapy (anti-TNF + thiopurine) was associated with an increased risk of opportunistic viral infections compared to anti-TNF monotherapy (1.3% *vs* 0.7%); no difference was found compared to thiopurine monotherapy (1.1%). Conversely, anti-TNF monotherapy was associated with a decreased risk of opportunistic viral infection compared to thiopurine monotherapy, suggesting that thiopurines drive the risk of opportunistic viral infections under combination therapy. These observations seem to agree with the AZA/6MP mechanism of action which primarily suppresses T lymphocytes activity that is involved in the prevention of viral infections.

With regard to corticosteroids, it is difficult to conclude their benefit and risk as they have many selection biases, as they are likely to be given to patients with severe disease, and there is heterogeneity in the type, dose and duration of their use. There are data suggesting that doses of prednisolone above 20 mg are associated with increased risk of bacterial and viral infections in IBD[35]. In patients with IBD exposed to thiopurines and anti-TNF agents, the increase in mortality from infection is negligible[17,36], instead, some studies have reported increased mortality in patients exposed to corticosteroids[34,37]. Case series recorded thiopurine-associated fatal infections, mainly in young patients. These infections include severe forms of varicella [38] and primary EBV or CMV infections complicated by hemophagocytic lymphohistiocytosis[39,40].

General approach

In immunocompromised patients, fever is sometimes the only manifestation of severe infection[41]. The approach in febrile patients must include exploration of their history and accurate physical examination. It is essential to recognize any symptoms or signs that can help identify the site of infection. Evaluation tests should include complete blood cell counts, C-reactive protein, serum procalcitonin (PCT), urine analysis and culture, VZV serology in patients without a reliable history of varicella immunization, hepatitis B virus (HBV) and hepatitis C virus (HCV), EBV and human immunodeficiency virus (HIV) serologies, stool examinations and strongyloidiasis serology (for returning travelers) and chest X-ray[12]. In the case of severe illness or when unusual pathogens are suspected, an infectious disease specialist should be involved.

In patients with respiratory symptoms (dyspnea, cough, purulent sputum, hemoptysis, pleuritic chest pain) or focal chest signs, a chest X-ray or chest ultrasound should be performed, and oxygen saturation determined. For patients with abnormal

Table 1 Summary of recommendations for the prevention and management of viral infections in inflammatory bowel disease

Infection	Screening prior to IM	Vaccination	Prophylaxis	Diagnosis	Therapy
HAV	IgG anti-HAV	Inactivated HAV vaccine; (2 doses, 0-6 mo)	-	IgG anti-HAV	Supportive
HCV	Ab anti-HCV; If positive HCV-RNA	-	-	Anti-HCV Ab; if positive HCV-RNA	DAA[62]
HBV	HBsAg, anti-HBs, anti-HBc;If positive HBV-DNA	Accelerated double-dose; (0, 1, 2 mo); If no response, re-vaccination; (0, 1, 2 mo) at a double-dose	In HBsAg+ (or antiHBc+); Entecavir 0.5 mg/d;Tenofovir, start 2 wk prior to IM	Exacerbation: ↑ AST/ALT; 100-fold rise HBV DNA	Entecavir 0.5-1 mg/daily; Tenofovir
HPV	Cervical smear test	bi/quadri/nine-valent;Women: 9-26 yr, Men: 11-23 yr	-	Cervical smear test	-
Influenza	-	Inactivated non-live trivalent	-	RT-PCR	Single neuraminidase inhibitor
HIV	HIV p24 Ag and Ab	-	-	Acute infection: RT-PCR	ART[99]
HSV	History of herpes lesions	-	Frequent/severe recurrence:acy-, valacy-, famci-clovir	Viral culture, H&E, RT-PCR	acyclovir, valacyclovir, and famciclovir
CMV	In steroid refractory patients	-	-	CMV inclusions in H&E + IHC followed by tissue RT- PCR	IV ganciclovir 5-7.5 mg/kg twice daily for 2 wk
VZV	VZV IgG/IgM	VZV vaccine: 4-3 wk before IM; HZ vaccine (recombinant): 2 doses, 0-3/6 mo	After exposure: VZV-Ig	RT-PCR on skin lesions	IV or PO acyclovir, valacyclovir, and famciclovir
EBV	EBV IgG/IgM	-	-	IgM VCA + and IgG EBNA -	-
SARS-CoV2	Recommended (test based on availability)	Recommended; mRNA-based; adenoviral vector	-	nasopharyngeal swabs; PCR-SARS-CoV-2	-

IM: Immune-modifier; DAA: Direct-acting antiviral; RT-PCR: Real-time polymerase chain reaction; IV: Intra-venous; PO: Per-os; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HPV: Human papillomavirus; HIV: Human immunodeficiency virus; HSV: Herpes simplex virus; CMV: Cytomegalovirus; VZV: Varicella zoster virus; EBV: Epstein-Barr virus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

oxygen saturation rates, computed tomography is required[42]. When a radiological and clinical picture of pneumonia is detected, an etiological diagnosis may be achieved by performing hemocultures, sputum cultures, nasopharyngeal swabbing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or influenza virus real-time polymerase chain reaction (RT-PCR), Legionella and pneumococcal urinary antigen or, in specific situations by bronchoalveolar lavage.

The persistence or relapses of gastrointestinal symptoms (diarrhea, rectal bleeding, abdominal pain and weight loss) may be due to exacerbation of the underlying IBD or enteric infections. As a first approach, a potential enteric infection should be ruled out. In this regard, stool cultures with examination for parasites and *Clostridium difficile* toxin testing are necessary[43]. Recently, different multiplex molecular assays (FilmArray Gastrointestinal GI Panel and Luminex xTAG Gastrointestinal Pathogen Panel, GPP) have been developed for the rapid identification of pathogens responsible for causing diarrheal illness, included Adenovirus F 40/41, Astrovirus, Norovirus GI/GII, Rotavirus A, and Sapovirus (I,II, IV, and V). Their adoption in clinical practice can improve the diagnostic efficiency of GI pathogens[44]. If stool microbiological analyses are negative, colonoscopy or recto-sigmoidoscopy with biopsies should be performed. HSV, and especially CMV, may be responsible for severe IBD relapses.

A lumbar puncture should be considered, under neurological advice, in patients with meningeal signs or encephalopathy, with strain culture or serology of cerebro-spinal fluid (CSF). CSF cultures are essential for the detection of bacterial pathogens. PCR of CSF is the gold standard for CMV, HSV, VZV, *Toxoplasma gondii* and John Cunningham virus (JCV) diagnosis. Magnetic resonance imaging should be performed for patients with mass forming lesions or encephalopathy and may be effective for diagnosing progressive multifocal leukoencephalopathy due to JCV, reported in the past for patients treated with natalizumab[45].

Dermatological manifestations of viral infections are mainly caused by HSV and VZV. The diagnosis of these conditions is usually based on clinical manifestations. Yet virological analysis can be performed directly on a recent lesion by PCR.

Diagnostic approaches for IBD patients with infectious symptoms are shown in Table 2.

IBD patients should follow all age-appropriate vaccinations as recommended by the Advisory Committee on Immunization Practices[46]. It is also important to respect the optimal timing of vaccination with regard to initiation of immunosuppressive therapy, as the use of immunosuppressive agents can lead to decreased immunogenicity of the vaccination[47,48].

In the case of minor infection (rhinitis, upper respiratory tract infection, *etc*.) with no risk of disseminated disease or rapid worsening, it is unnecessary to withdraw immunomodulators. However, in the case of risk for disseminated or uncontrolled disease (shingles, viral pneumonia, encephalitis), high-grade fever and infection with a well-known mortality risk, withdrawal of immunomodulators are best advised at the peak of infection, and the decision to resume immunomodulator treatment is on a case-by-case basis and a multidisciplinary approach[49].

VIRAL DISEASES

Hepatitis A virus

Hepatitis A virus (HAV) is responsible for hepatitis A infection, which is usually a mild, self-limited disease that does not become chronic. It is transmitted by the fecal-oral route, and poor hygienic and socioeconomic conditions promote this infection[50,51]. Infection confers lifelong immunity and is preventable *via* vaccination. The onset of symptoms is sudden, with malaise, asthenia, nausea, vomiting, and pain in the upper abdominal quadrants. No specific disease manifestations in immunocompromised hosts have been described. The most relevant biochemical alteration is the increase in transaminases (often > 1000 IU/dL) and, generally, precedes the increase in bilirubin (typically ≤ 10 mg/dL). The presence of IgM anti-HAV antibodies allows the etiological diagnosis. The American College of Gastroenterology and the Korean Association for the Study of Intestinal Diseases recommend a test for HAV (IgG anti-HAV antibodies) in patients with IBD. In those who are negative, vaccination should be recommended[52,53]. On the other hand, ECCO guidelines suggest vaccination only in high-risk subjects and those traveling to endemic areas[12]. Inactivated hepatitis A vaccines should be preferred[54], as they have high, long-lasting immunogenicity with few side effects[55]. Since immunosuppressive therapy can lower the seroconversion rate[56], optimal timing for HAV vaccination is at IBD diagnosis or before starting immunosuppressive therapy, even if administration is acceptable during maintenance therapy. The vaccine should be administered in 2 doses with an interval of 6 mo.

HCV

The global HCV prevalence is estimated at 2.5%, ranging from 2.9% in Africa and 1.3% in the Americas[57]. In Europe it is estimated that 0.2-2% of the population is infected with HCV. The prevalence of HCV in patients with IBD is comparable to that in the general population[58-61]. HCV is typically transmitted parenterally. Acute HCV infection is often asymptomatic and chronic HCV infection develops in about 85% of all cases. Among patients with chronic HCV infection, 20% develop liver cirrhosis within 20 years of disease duration, with a high rate of incidence of hepatocellular carcinoma. General measures to reduce or prevent HCV infection are appropriate since vaccination and prophylactic treatment are not available. The ECCO guidelines suggest performing HCV screening before starting treatment with immune-modifying drugs for IBD. Testing should be performed by searching for anti-HCV antibodies and, if antibodies are positive, by identification of HCV-RNA[62,63]. Management of HCV in this population is important as immunosuppression may precipitate HCV-associated liver damage[64] and immunomodulators may result in cumulative liver toxicity[65,66]. If infection is confirmed, patients should be treated according to the HCV clinical practice guidelines[64], possibly before starting biologics or immunomodulator therapy. However, the timing strategy for treating HCV-infected IBD subjects could depend on several factors, including the IBD activity and patient's comorbidities. If HCV-infected patients with IBD cannot delay their immune-modifying therapy, their liver function should be monitored closely. There are no data to suggest that biologics are associated with reactivation or exacerbation of the course

Table 2 Diagnostic approach to inflammatory bowel disease patients with infectious symptoms

Symptoms cluster	Potential viral pathogens	Diagnostic work up
Fever	VZV, HBV, HCV, EBV, HIV, SARS-CoV-2	Medical history, physical examination
		Blood cell counts, PCR, PCT
		VZV, HBV, HCV, EBV and HIV Ab
		Hemocultures
		Urine analysis and culture
		Stool examinations
		Strongyloidiasis serology
		Chest X-ray
		Infectious disease specialist consult
Respiratory	Influenza, SARS-CoV-2 (Bilateral interstitial infiltrates)	Chest X-ray or US
		SaO_2% < range → CT
		Pneumonia:
		Sputum cultures
		NPS for SARS-CoV-2/influenza virus Legionella and pneumococcal U-Ag
		Bronchoalveolar lavage
Gastrointestinal	HSV, CMV, EBV, Adenovirus, Astrovirus, Norovirus, Rotavirus, Sapovirus	Rule out potential enteric infection:
		Stool cultures
		Examination for parasites
		C. difficile toxin testing
		Multiplex molecular assays
Central nervous system	CMV, HSV, VZV, JC virus	Neurological advice
		CSF cultures and PCR
		MRI
Cutaneous	HSV, VZV	Dermatological consult
		PCR on recent lesion

CRP: C-reactive protein; PCT: Procalcitonin; US: Ultrasound; CT: Computed tomography; NPS: Nasopharyngeal swab; U-Ag: Urinary antigen; CSF: Cerebrospinal fluid; PCR: Polymerase chain reaction; MRI: Magnetic resonance imaging; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HPV: Human papillomavirus; HIV: Human immunodeficiency virus; HSV: Herpes simplex virus; CMV: Cytomegalovirus; VZV: Varicella zoster virus; EBV: Epstein-Barr virus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; JC: John Cunningham virus; *C. difficile*: *Clostridium difficile*.

of HCV and the safety profile of anti-TNF-α agents in HCV patients is good, even if there seems to be variances in the hepatotoxic profile between different biologics[59,66,67].

HBV

HBV is carried globally by 248 million people. HBsAg seroprevalence is 3.61% and it varies by country and region, from 2% in areas with low prevalence (UK, Canada, Western Europe, *etc.*), 2%-7% in those with moderate prevalence (South Korea, Mediterranean countries, Japan, Central Asia, Middle East, and parts of South America), and more than 8% in countries of the African region, which have the highest endemicity[68,69]. The prevalence of HBV in patients with IBD is similar to that in the general population[61,70]. HBV can manifest as acute and chronic infection. In the acute phase, the infection can manifest as jaundiced or non-jaundiced hepatitis (high levels of HBV DNA are associated with increased transaminases, with varying degrees of bilirubin elevation) and in more severe cases as fulminant hepatitis. The chronic phase has various patterns of expression, from asymptomatic carrier to the sequence chronic hepatitis, liver cirrhosis and related hepatocellular carcinoma. Patients with

IBD should be assessed for HBV infection (HBsAg, anti-HBs, anti-HBc) or immunization status. Anti-core antibodies could represent the only indicator in patients with HIV or HCV co-infections[71]. In patients diagnosed with HBV infection, HBeAg, anti-HBe, and HBV DNA should also be assessed[12] and then referred to a specialist for diagnosis of the phase of HBV infection. Vaccination of seronegative (anti-HBs -, anti-HBc -) patients is recommended. Patients with IBD on immunosuppression demonstrated a significantly reduced response to the standard vaccination (rHBAg 20 μg single dose at 0, 1 and 6 mo) as compared with the general population[72] (64% adequate immune response and 40% effective immune response)[73]. Receiving an accelerated double-dose at 0, 1, 2 mo followed by revaccination (0, 1, and 2 mo) at a double-dose if no adequate response is achieved has demonstrated better efficacy than the standard schedule[74,75]. Serology testing 1 to 2 mo after administration of the last dose are required to assess the need for revaccination and check-ups for anti-HBs yearly or every 2 years seems to be good practice[12,76]. A single booster dose should be given to immunocompromised patients who lose seroprotection[77].

The risk of viral reactivation in HBV is increased in patients who are receiving immune-modifying therapy and are HBsAg-positive or HBsAg-negative plus anti-HBc positive[64], in a manner that is proportional to the level of immunosuppression achieved[65,78]. Liver dysfunction has been described in retrospective studies in 25%-36% of HBsAg-positive patients with IBD receiving immunosuppressive agents; HBV reactivations have been associated with hepatic decompensation in a considerable proportion of cases[79,80]. Recognized risk factors were treatment with 2 or more immunomodulators for a long period of time, presence of HBV DNA and avoidance of antiviral prophylaxis. TNF-α and related cytokines are important in regulating hepatitis B replication and anti-TNF treatments confer a high risk of HBV reactivation [81,82].

Exacerbation of HBV infection is recognized by an increase in transaminases associated with high levels of serum HBV DNA (100-fold rise compared to baseline) in patients with chronic hepatitis B. HBsAg positive patients should receive prophylactic antiviral treatment with nucleotide/nucleoside analogues with a high barrier to resistance (*i.e.* entecavir or tenofovir), best started 2 wk prior to the introduction of immunomodulators or a biologic and continued for 12 mo after their withdrawal.

Relapse of past HBV infection is detected based on reverse seroreversion from HBsAg-negativity to HBsAg-positivity, or on the detection of serum HBV DNA in patients who are HBsAg-negative plus anti-HBc-positive. Relapse of occult HBV has been described in IBD and rheumatology patients treated with anti-TNF and corticosteroids or DMARDs[83,84], but this rarely occurs[59,79]. The preventive approach in patients with HBsAg negative and anti-HBc positive varies among the published guidelines. The American Gastroenterological Association suggest antiviral prophylaxis for patients treated with anti-TNF-α or with corticosteroids[85]. The ECCO, according to the European Association for the Study of the Liver, recommends active monitoring of AST/ALT levels and the virus markers (HBsAg and/or HBV DNA) every 1-3 mo with antiviral therapy once HBV DNA or seroreversion is detected (preemptive therapy strategy)[12,64].

Human papillomavirus

Human papillomavirus (HPV) is a sexually transmitted infection. There are approximately 40 serotypes of HPV classified into low-risk serotypes and high-risk serotypes, which are associated with cervical and anal squamous cell carcinoma[86]. HPV also causes cutaneous warts. There are reports of an increased frequency of HPV-related anogenital warts in patients receiving AZA[30], but not anti-TNF[87]. IBD has not been associated with the development of cervical cancer; however, patients with CD who smoke, are younger at diagnosis, and those who use thiopurines or methotrexate combined with corticosteroids might be more at risk[88,89]. Other immunosuppressive medications, in particular anti-TNF therapy, seem not to have an increased risk. However, the quality of evidence is poor, physician awareness and prevention by lifestyle counseling, HPV vaccination and screening are warranted[90]. There are three types of HPV vaccine: bivalent, Cervarix, comprising 16, 18 serotypes, quadrivalent, Silagard, and Gardasil, with 6, 11, 16, 18 serotypes, and nine-valent, Gardasil 9, with 6, 11, 16, 18, 31, 33, 45, 52, 58 serotypes. As the HPV vaccines do not contain live viruses, they may be administered to an immunosuppressed patient with an excellent safety profile and immunogenicity[91]. The vaccine is indicated for women aged 9 to 26 years, preferably before the first sexual intercourse but also after initiation of sexual activity. Male patients should be vaccinated at the age of 11 to 12 years, and catch-up for those aged 13 to 21 years. Of note, cervical screening recommendations are similar for vaccinated and nonvaccinated women. In IBD patients, a cervical smear test should

be performed initially at the time of diagnosis, and if normal then annually[12]. Different studies have shown an unsatisfactory cervical cancer screening rate and inadequate HPV vaccine coverage among IBD patients[92-94] advising that better cooperation between patients and physicians is required to improve education on preventive measures. Management of abnormal findings at cervical smears includes colposcopic examination with biopsy/brushing, and eventually conization.

Influenza virus

There are two types of influenza virus: type A and type B, which cause seasonal epidemics of acute respiratory illness. IBD patients have an increased risk of influenza compared with those without IBD with a higher rate of hospitalization, often with bacterial pneumonia superinfection[95,96]. Patients requiring hospitalization for possible influenza infection should be tested. The gold standard for diagnosis of influenza is RT-PCR testing in specimens from different respiratory sites[97]. In the outpatient setting, diagnosis is made with a high likelihood by clinical criteria alone. Inactivated non-live trivalent influenza vaccination is recommended annually in the fall and spring for IBD patients and their household contacts to prevent influenza virus infection. Live attenuated influenza vaccine is not recommended for patients on immunomodulators[12]. IBD patients treated with anti-TNF alone or combined with thiopurine, may have a reduction in the influenza seroprotection rate after inactivated non-live trivalent influenza vaccination[98-100]; however, it is sufficient to warrant annual influenza vaccination. Antiviral treatment (single neuraminidase inhibitor; either oral oseltamivir, inhaled zanamivir, or intravenous peramivir) should be started as soon as possible for patients with documented or suspected influenza, who are taking immunomodulator therapy, especially if older than 65 years[97].

HIV

HIV belongs to the human retrovirus family. HIV infection causes a wide range of clinical consequences varying from asymptomatic to severe opportunistic diseases due to immunosuppression, including infections and malignancies, which are characterized by acquired immunodeficiency syndrome (AIDS). HIV infection is usually transmitted through sexual intercourse, exposure to infected blood, or perinatal transmission. Antiretroviral therapy (ART) effectively suppresses viral replication so that an almost normal immune status can be regained, leading to dramatic reductions in morbidity and mortality. For most individuals, an ART regimen consists of a dual nucleoside combination plus a third agent from a different class[101]. Patients with IBD and HIV infection have shown controversial data concerning the remission hypothesis of IBD due to CD4 count depletion caused by HIV[102]. A recent multicenter retrospective cohort study suggested that HIV infection might attenuate the IBD course as HIV-infected patients need fewer immunosuppressants and biologics to control the disease[103]. In a previous analysis, over a median follow-up of 8.4 years, HIV status was the only risk factor independently associated with a lower probability of IBD relapse[104]. However, evidence of the interrelation between HIV and IBD remains poorly understood. The diagnosis of IBD in HIV infection can be complex because of possible symptom overlap[105]. The differential diagnosis includes a multitude of etiologies from protozoic, fungal, viral, and bacterial pathogens (HSV, AIDS-related CMV gastrointestinal disease[106-108], Salmonella, Shigella, Campylobacter, *Mycobacterium tuberculosis*, Histoplasma or Cryptococcus) to malignancy (lymphoma or Kaposi's sarcoma[109]) to medications (ART-associated diarrhea[110,111]). The entity known as AIDS enteropathy can be diagnosed once other causes of diarrhea are investigated and excluded[112]. It is expected that all cases of IBD in HIV infection require biopsy confirmation by an expert gastrointestinal pathologist. All IBD patients undergoing immunomodulator or biological therapy should receive testing for HIV infection (HIV p24 antigen and antibody testing, with PCR if acute infection is suspected) to exclude unknown infection. Experiences in treating individuals with HIV infection with anti-TNF therapies are limited. It is possible to prescribe with a reasonable ratio of benefits to risks if the patients have a low HIV viral load and are not severely immunosuppressed (>350 CD4 cells/μL), keeping them closely monitored[103,113-115].

HSV

HSV type 1 (HSV-1) and HSV type 2 (HSV-2) are common infections worldwide. HSV-1 is implicated in most cases of orofacial herpes lesions ("cold sores"), while HSV-2 causes most cases of recurrent genital herpes[116]. After primary infection, HSV establishes chronic infection in neural ganglia and reactivates on mucosa and skin;

infection is lifelong. Especially in immunocompromised hosts, HSV infection may cause severe manifestations, including encephalitis, meningitis[117], hepatitis[118], respiratory tract infections[119,120], esophagitis[121-123] and proctitis[124-126]. Within the treatment regimens for IBD, corticosteroids and azathioprine have been related to skin or genital herpetic flares[30,127]. Extended HSV colitis associated with IBD exacerbations are largely reported[128-132]. The testing approach depends upon the site of the disease (mucocutaneous, ocular, neurologic or visceral). HSV can be diagnosed, either by isolating the virus in a culture of the affected tissue or by histopathological examination showing nucleated ground-glass herpes inclusions in the cells. HSV PCR is an alternative, but more sensitive method to confirm HSV infection. Before starting with immunosuppressive drugs, previous history of HSV infection should be investigated, but serological screening is unnecessary[12]. Frequent and severe recurrence of HSV disease can be prevented by therapy with oral acyclovir (400-800 mg twice or thrice daily), valacyclovir (500 mg daily) or famciclovir (500 mg twice daily).

CMV

With a worldwide prevalence of over 80%[133], CMV causes in most subjects asymptomatic or mononucleosis-like syndrome during primary infections, persisting lifelong in a latent form in different organs, including the gut[134]. Especially in immunocompromised patients, CMV can reactivate, causing tissue-invasive end-organ damage, mainly in the brain, lung, retina and digestive tract. CMV colitis in IBD patients should be considered. Seroprevalence (CMV IgG) in IBD patients is comparable to that in the general population[135,136]. On the contrary, identification of CMV viral DNA in the mucosa was reported, from limited data, to be more prevalent in patients with IBD than in healthy controls[137,138]. CMV tissue reactivation is rare in CD flares, whereas it is frequent in UC[139]. Characteristics that increase the risk of CMV reactivations in IBD and develop colitis flare include female sex, pancolitis[140,141], advanced age[142], and disease duration less than 60 mo. Immunomodulator therapy with azathioprine[140,143] and steroids[142,144] is a recognized trigger factor, while on chronic anti-TNF, the data is conflicting[145-148]. Screening for subclinical CMV infection in IBD patients is not required unless the patient is steroid-refractory[12]. Patients with CMV infection and severe acute colitis, in fact, show a higher probability of steroid resistance[135,136,149] and enhanced risk for colectomy[150,151] than non-infected patients. Colonic CMV infection can be diagnosed by hematoxylin and eosin (H&E) or immunohistochemical staining (IHC) histology, serology assay, polymerase chain reaction (PCR) for CMV DNA in peripheral blood or tissue (from targeted biopsies taken from the ulcer base), and CMV antigenemia (pp65)[152]. The gold standard for diagnosing CMV overinfection is the identification of CMV inclusions (typically basophilic intranuclear inclusions) or positive CMV-specific immunohistochemistry staining on histopathology[153], eventually followed by tissue-direct PCR for viral load quantification. CMV infection cannot be excluded based on a negative whole-blood PCR result[154]. In patients who are steroid-dependent or refractory[155] and those with high CMV viral load in colonic tissue[156], antiviral therapy is recommended. Several agents are available for CMV infection, including ganciclovir, valganciclovir and foscarnet. The most used antiviral agent is intravenous ganciclovir at a dose of 5-7.5 mg/kg twice daily for 2 wk [152]. ECCO guidelines allow a course of intravenous ganciclovir 5 mg/kg twice for 3-5 days, followed by oral valganciclovir at 900 mg *per os* twice daily for 2-3 wk[12]. Foscarnet (for 2-3 wk) is an alternative in case of resistance or intolerance (hematologic or renal toxicity). Overall, there is a lack of knowledge to give recommendations on managing immunosuppressant medications during or after treatment of CMV colitis. Inducing remission with anti-TNF and tapering off the steroids while continuing intravenous ganciclovir may be an acceptable strategy[152].

VZV

VZV causes varicella (chickenpox) during its primary infection, and after decades of latency in sensory ganglia, it maintains the potential for reactivation as herpes zoster (shingles). Primary infection is generally a mild-moderate disease in most children. However, it can be life-threatening in adults (especially during pregnancy) and immunocompromised patients, potentially leading to severe complications such as central nervous system involvement, pneumonia, secondary bacterial infections, and death[157]. At diagnosis, all IBD patients (unless those with documented vaccination history) should be tested for VZV IgG serology[158]. Corticosteroids, thiopurines, methotrexate, and anti-TNF in monotherapy or even more in combination, are recognized risk factors for varicella infection[159,160]. The literature describes 23 cases

of varicella in IBD patients receiving immunosuppressants and the fatality rate is reported to be 22%[161]. Diagnosis is based on clinical signs (fever and typical vesicular lesions in different stages of development on the face, trunk, and extremities), or real-time PCR on samples taken from skin lesions in an immunocompromised host or in the evaluation of atypical lesions[162]. In immunocompromised hosts with active varicella lesions, antiviral therapy is recommended in order to reduce the severity of symptoms and the risk of serious complications. Oral valacyclovir (1 g 3 times daily) may be considered in patients with mild disease followed closely. For most patients, initial therapy with intravenous acyclovir (10 mg/kg every 8 h) is suggested, with the possibility of switching to oral antiviral after defervescence in the absence of visceral involvement. The treatment duration is 7-10 days, and it has to be continued until all lesions have crusted. After significant exposure, primary prophylaxis with VZV immune globulin within 10 days is indicated in IBD patients receiving immunosuppressive therapy since they are ineligible for varicella vaccine prophylaxis[163]. From a prevention perspective, as the VZV vaccine is a live vaccine, its administration (2 doses, 1 mo apart) should be carried out at least 4-3 wk before starting immunosuppressive therapy[12,52] or 3-6 mo after stopping it.

IBD patients are also at increased risk of developing herpes zoster (HZ). Due to diffuse concurrent use of immunosuppressant agents, clinical manifestations are often more severe, and the risk of complications such as post-herpetic neuralgia, central nervous system and ocular involvement are enhanced[164,165]. Corticosteroids and thiopurines (especially in combination with anti-TNF medication) are known risk factors linked to HZ infection[32,33,166]. Recently tofacitinib has also been observed to be related in a dose-dependent manner to HZ, with additional risk conferred by older age, diabetes mellitus, corticosteroids therapy and prior anti-TNF failure[167,168]. The diagnosis of HZ is usually based on the clinical presentation (unilateral, usually painful vesicular-papular eruption with a defined dermatomal distribution). However, since immunocompromised subjects may have an atypical presentation (hemorrhagic skin lesions affecting multiple dermatomes), real-time PCR may confirm the diagnosis. Antiviral therapy must be started in IBD patients with HZ, even after 72 h from presentation. Patients with disseminated HZ should be hospitalized for intravenous acyclovir therapy (10 mg/kg every 8 h). On the other hand, oral therapy is usually sufficient for the initial treatment of uncomplicated HZ. Regimen options last 7 days and include valacyclovir (1 g 3 times daily), famciclovir (500 mg 3 times daily) and acyclovir (800 mg 5 times daily). Two types of zoster vaccine are available: the first one is a live attenuated vaccine, which is contraindicated in patients receiving moderate or high-dose immunosuppressive therapy and recently a new recombinant glycoprotein E vaccine has become available. The vaccine is administered twice, at 0 and 2-6 mo. Recombinant vaccine has been proven to be highly effective in reducing HZ risk and postherpetic neuralgia among adult subjects[169]; thus, the ACIP recommends it for use in immunocompetent adults aged ≥ 50 years[170]. There are insufficient data to make recommendations regarding zoster vaccination in immunosuppressed patients, but initial evidence suggests good safety and immunogenic profile in this subgroup of patients[171-173]. Therefore, it seems to be an acceptable strategy, to propose recombinant vaccine in patients with uncontrolled severe disease activity, history of shingles, a scheduled therapy with tofacitinib, treated with azathioprine and aged > 40 years, and to all patients aged > 50 years[161].

EBV

EBV is a ubiquitous herpesvirus with a seroprevalence >90% worldwide. It is responsible for infectious mononucleosis (IM), and after primary infection persists asymptomatically lifelong in latently-infected circulating B-lymphocytes[174]. EBV infection is associated with different types of malignancies, including B cell lymphomas, T cell lymphomas, Hodgkin lymphoma and nasopharyngeal carcinomas [175-177]. The incidence rate of lymphoproliferative disorders is much higher in IBD patients than in the general population. The relationship between immunosuppressive drugs (in particular, evidence seems to suggest that thiopurines have specific additional risks[178,179]) and EBV infection may be implicated in the pathogenesis of this disease[180,181]. In addition, severe EBV diseases such as fatal infectious mononucleosis and hemophagocytic lymphohistiocytosis occur when primary infection develops in immunosuppressed patients[182-184]. Therefore, it seems relevant to determine EBV serology status by testing EBV IgG before starting immunomodulator therapy. In EBV seronegative patients, anti-TNF monotherapy should be preferred over thiopurines[12]. The diagnosis of acute EBV infection is made in the presence of IgM VCA and the absence of IgG EBNA antibodies. When primary infection is recognized, immunomodulator therapy should be reduced or discontinued

if possible. Advice from a hematologist/oncologist is required when lymphoproliferative disease is suspected.

SARS-CoV-2 (coronavirus disease 19)

On March 11th, 2020 the World Health Organization declared coronavirus disease 19 (COVID-19) a global pandemic, marking one of the most intense passages in recent history. The range of symptomatic infection goes from mild to critical; >80% of cases are not severe[185], but morbidity and mortality are not negligible. Current evidence shows that the IBD population does not have an increased prevalence of SARS-CoV-2 infection[186-188] and immunomodulators, biologics, or Janus Kinase inhibitors do not represent a risk factor for SARS-CoV-2 infection and more severe COVID- 19[189,190]. On the other hand, in several studies of IBD patients with COVID-19, a trend towards an adverse outcome with concomitant corticosteroids was reported[191]. COVID-19 may occur early with gastrointestinal symptoms (anorexia, nausea, vomiting, abdominal pain, and diarrhea)[192] simulating IBD manifestations. For that reason, patients with a suspected IBD flare should be tested to exclude SARS-CoV-2 infection, especially before initiation of biologics[193]. When IBD patients are diagnosed with COVID-19, in its current state, several consensuses and expert opinions propose discontinuation of thiopurines, methotrexate, and JAK inhibitors and extend the interval of administration for biological drugs until nasopharyngeal swab PCR-SARS-CoV-2 tests results are negative or 3 after days of no fever and clinical improvement [194,195]. Since IBD patients were ruled out of the SARS-CoV-2 vaccine clinical trials, questions regarding the safety and effectiveness in patients with IBD are currently unanswered. As the COVID-19 vaccines available use mRNA-based technology (Pfizer/Biontech, ModeRNA) or non-replicating adenoviral vectors expressing the spike protein (AstraZeneca/Oxford, J&J, Sinovac, Sputnik V) the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) recommends vaccinating all patients with IBD as soon as they are able to receive the vaccine, regardless of immune-modifying therapies[196]. The exception is for any live-attenuated virus vaccines or replication-competent viral vector vaccines that may come to market. Even The British Society of Gastroenterology agrees, strongly supporting SARS-CoV-2 vaccination in patients with IBD, underlining that the critical concerns in patients taking immunosuppressive drugs are more related to the risk of suboptimal immunization rather than the vaccine safety profile[197].

CONCLUSION

Due to the alterations in the immune response and the growing adoption of immunomodulators and biologics, IBD patients represent a population exposed to opportunistic infections. The risk of infections is also aggravated by an insufficient immunization status as too frequently observed in patients with IBD. In this field, gastroenterologists should be aware of viral infections that may complicate the IBD course, as they are often challenging to diagnose and treat. Moreover, excess hospitalizations due to viral infections and their related costs, contribute to the human and financial burden of IBD. Prevention is the most important step; a careful workup aimed at avoiding viral infectious disease is essential. Anamnestic and serological screening should be performed in all patients before starting immunosuppressive therapy. In addition, assessing and completing the vaccination status in IBD patients, ideally before immunosuppressive therapy, is the new standard of care. It is also important to provide prophylaxis when indicated to avoid the occurrence of potentially preventable infection. Continued vigilance and a high degree of suspicion is required to monitor for viral infection during maintenance therapy. Even if a direct correlation between a specific immunosuppressant drug and viral infection is not established, special attention must be paid to patients receiving corticosteroids, thiopurines, or combination therapy with thiopurines and anti-TNF agents as they are more prone to contracting opportunistic viral infections, in particular HSV, VZV, CMV, and EBV. It seems prudent to minimize the use of systemic steroids, think of alternatives to steroids and, if used, taper to the lowest possible dose quickly. As a matter of course, long-term steroids are contraindicated to avoid the risk of viral infection. Early diagnosis and appropriate treatment are necessary to prevent potentially severe complications that could precipitate the disease course if infective complications occur. Multidisciplinary cooperation between the gastroenterologist, infectious disease specialist and primary care physicians is the best way to optimize the care provided to IBD patients. The most significant gaps in knowledge in this area

are related to the difficulty in stratifying high-risk patients who may benefit from personalized preventive or therapeutic interventions. Prospective randomized controlled trials focused on IBD patients who are diagnosed with viral infection should be planned.

REFERENCES

1 **Li N**, Shi RH. Updated review on immune factors in pathogenesis of Crohn's disease. *World J Gastroenterol* 2018; **24**: 15-22 [PMID: 29358878 DOI: 10.3748/wjg.v24.i1.15]

2 **Torres J**, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, Adamina M, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, El-Hussuna A, Ellul P, Frei-Lanter C, Furfaro F, Gingert C, Gionchetti P, Gomollon F, González-Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Lytras T, Maaser C, Magro F, Marshall JK, Myrelid P, Pellino G, Rosa I, Sabino J, Savarino E, Spinelli A, Stassen L, Uzzan M, Vavricka S, Verstockt B, Warusavitarne J, Zmora O, Fiorino G. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis* 2020; **14**: 4-22 [PMID: 31711158 DOI: 10.1093/ecco-jcc/jjz180]

3 **Peyrin-Biroulet L**, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, D'Haens G, Dotan I, Dubinsky M, Feagan B, Fiorino G, Gearry R, Krishnareddy S, Lakatos PL, Loftus EV Jr, Marteau P, Munkholm P, Murdoch TB, Ordás I, Panaccione R, Riddell RH, Ruel J, Rubin DT, Samaan M, Siegel CA, Silverberg MS, Stoker J, Schreiber S, Travis S, Van Assche G, Danese S, Panes J, Bouguen G, O'Donnell S, Pariente B, Winer S, Hanauer S, Colombel JF. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol* 2015; **110**: 1324-1338 [PMID: 26303131 DOI: 10.1038/ajg.2015.233]

4 **Colombel JF**, D'haens G, Lee WJ, Petersson J, Panaccione R. Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. *J Crohns Colitis* 2020; **14**: 254-266 [PMID: 31403666 DOI: 10.1093/ecco-jcc/jjz131]

5 **Neurath MF**, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut* 2012; **61**: 1619-1635 [PMID: 22842618 DOI: 10.1136/gutjnl-2012-302830]

6 **Frøslie KF**, Jahnsen J, Moum BA, Vatn MH; IBSEN Group. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007; **133**: 412-422 [PMID: 17681162 DOI: 10.1053/j.gastro.2007.05.051]

7 **Cucchiara S**, D'Arcangelo G, Isoldi S, Aloi M, Stronati L. Mucosal healing in Crohn's disease: new insights. *Expert Rev Gastroenterol Hepatol* 2020; **14**: 335-345 [PMID: 32315209 DOI: 10.1080/17474124.2020.1759416]

8 **Schnitzler F**, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 1295-1301 [PMID: 19340881 DOI: 10.1002/ibd.20927]

9 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]

10 **Shah SC**, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. *Aliment Pharmacol Ther* 2016; **43**: 317-333 [PMID: 26607562 DOI: 10.1111/apt.13475]

11 **Toruner M**, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, Colombel JF, Egan LJ. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008; **134**: 929-936 [PMID: 18294633 DOI: 10.1053/j.gastro.2008.01.012]

12 **Rahier JF**, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, Cottone M, de Ridder L, Doherty G, Ehehalt R, Esteve M, Katsanos K, Lees CW, Macmahon E, Moreels T, Reinisch W, Tilg H, Tremblay L, Veereman-Wauters G, Viget N, Yazdanpanah Y, Eliakim R, Colombel JF; European Crohn's and Colitis Organisation (ECCO). Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014; **8**: 443-468 [PMID: 24613021 DOI: 10.1016/j.crohns.2013.12.013]

13 **Bonovas S**, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet L, Danese S. 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**: 1385-1397. e10 [PMID: 27189910 DOI: 10.1016/j.cgh.2016.04.039]

14 **Nyboe Andersen N**, Pasternak B, Friis-Møller N, Andersson M, Jess T. Association between tumour necrosis factor-α inhibitors and risk of serious infections in people with inflammatory bowel disease: nationwide Danish cohort study. *BMJ* 2015; **350**: h2809 [PMID: 26048617 DOI: 10.1136/bmj.h2809]

15 **Gong SS**, Fan YH, Han QQ, Lv B, Xu Y. Nested case-control study on risk factors for opportunistic infections in patients with inflammatory bowel disease. *World J Gastroenterol* 2019; **25**: 2240-2250 [PMID: 31143074 DOI: 10.3748/wjg.v25.i18.2240]

16 **Lawrance IC**, Radford-Smith GL, Bampton PA, Andrews JM, Tan PK, Croft A, Gearry RB, Florin TH. Serious infections in patients with inflammatory bowel disease receiving anti-tumor-necrosis-factor-alpha therapy: an Australian and New Zealand experience. *J Gastroenterol Hepatol* 2010; **25**: 1732-1738 [PMID: 21039834 DOI: 10.1111/j.1440-1746.2010.06407.x]

17 **Lichtenstein GR**, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, Pritchard ML, Sandborn WJ. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006; **4**: 621-630 [PMID: 16678077 DOI: 10.1016/j.cgh.2006.03.002]

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**: 337-346. e10 [PMID: 29655835 DOI: 10.1053/j.gastro.2018.04.012]

19 **Piovani D**, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Bonovas S. Systematic review with meta-analysis: biologics and risk of infection or cancer in elderly patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2020; **51**: 820-830 [PMID: 32170782 DOI: 10.1111/apt.15692]

20 **Rahier JF**, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, Domènech E, Eliakim R, Eser A, Frater J, Gassull M, Giladi M, Kaser A, Lémann M, Moreels T, Moschen A, Pollok R, Reinisch W, Schunter M, Stange EF, Tilg H, Van Assche G, Viget N, Vucelic B, Walsh A, Weiss G, Yazdanpanah Y, Zabana Y, Travis SP, Colombel JF; 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 [PMID: 21172250 DOI: 10.1016/j.crohns.2009.02.010]

21 **Wisniewski A**, Kirchgesner J, Seksik P, Landman C, Bourrier A, Nion-Larmurier I, Marteau P, Cosnes J, Sokol H, Beaugerie L; the Saint-Antoine IBD network. Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. *United European Gastroenterol J* 2020; **8**: 303-313 [PMID: 32529821 DOI: 10.1177/2050640619889763]

22 **Cottone M**, Kohn A, Daperno M, Armuzzi A, Guidi L, D'Inca R, Bossa F, Angelucci E, Biancone L, Gionchetti P, Ardizzone S, Papi C, Fries W, Danese S, Riegler G, Cappello M, Castiglione F, Annese V, Orlando A. 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**: 30-35 [PMID: 20951835 DOI: 10.1016/j.cgh.2010.09.026]

23 **Gavazzi G**, Krause KH. Ageing and infection. *Lancet Infect Dis* 2002; **2**: 659-666 [PMID: 12409046 DOI: 10.1016/S1473-3099(02)00437-1]

24 **Simonsen L**. The global impact of influenza on morbidity and mortality. *Vaccine* 1999; **17** Suppl 1: S3-10 [PMID: 10471173 DOI: 10.1016/s0264-410x(99)00099-7]

25 **Schmader K**. Herpes zoster in older adults. *Clin Infect Dis* 2001; **32**: 1481-1486 [PMID: 11317250 DOI: 10.1086/320169]

26 **Garibaldi RA**. Residential care and the elderly: the burden of infection. *J Hosp Infect* 1999; **43** Suppl: S9-18 [PMID: 10658754 DOI: 10.1016/S0195-6701(99)90061-0]

27 **Sager K**, Alam S, Bond A, Chinnappan L, Probert CS. Review article: cytomegalovirus and inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; **41**: 725-733 [PMID: 25684400 DOI: 10.1111/apt.13124]

28 **Siegmund B**. Cytomegalovirus infection associated with inflammatory bowel disease. *Lancet Gastroenterol Hepatol* 2017; **2**: 369-376 [PMID: 28397701 DOI: 10.1016/S2468-1253(16)30159-5]

29 **Reijasse D**, Le Pendeven C, Cosnes J, Dehee A, Gendre JP, Nicolas JC, Beaugerie L. Epstein-Barr virus viral load in Crohn's disease: effect of immunosuppressive therapy. *Inflamm Bowel Dis* 2004; **10**: 85-90 [PMID: 15168806 DOI: 10.1097/00054725-200403000-00004]

30 **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**: 1106-1113 [PMID: 19222411 DOI: 10.1111/j.1365-2036.2009.03973.x]

31 **Gupta G**, Lautenbach E, Lewis JD. Incidence and risk factors for herpes zoster among patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006; **4**: 1483-1490 [PMID: 17162240 DOI: 10.1016/j.cgh.2006.09.019]

32 **Long MD**, Martin C, Sandler RS, Kappelman MD. Increased risk of herpes zoster among 108 604 patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **37**: 420-429 [PMID: 23240738 DOI: 10.1111/apt.12182]

33 **Khan N**, Patel D, Trivedi C, Shah Y, Lichtenstein G, Lewis J, Yang YX. Overall and Comparative Risk of Herpes Zoster With Pharmacotherapy for Inflammatory Bowel Diseases: A Nationwide Cohort Study. *Clin Gastroenterol Hepatol* 2018; **16**: 1919-1927. e3 [PMID: 29309905 DOI: 10.1016/j.cgh.2017.12.052]

34 **Lewis JD**, Scott FI, Brensinger CM, Roy JA, Osterman MT, Mamtani R, Bewtra M, Chen L, Yun H, Xie F, Curtis JR. Increased Mortality Rates With Prolonged Corticosteroid Therapy When Compared With Antitumor Necrosis Factor-α-Directed Therapy for Inflammatory Bowel Disease. *Am J Gastroenterol* 2018; **113**: 405-417 [PMID: 29336432 DOI: 10.1038/ajg.2017.479]

35 **Dorrington AM**, Selinger CP, Parkes GC, Smith M, Pollok RC, Raine T. The Historical Role and Contemporary Use of Corticosteroids in Inflammatory Bowel Disease. *J Crohns Colitis* 2020; **14**: 1316-1329 [PMID: 32170314 DOI: 10.1093/ecco-jcc/jjaa053]

36 **Hutfless SM**, Weng X, Liu L, Allison J, Herrinton LJ. Mortality by medication use among patients

with inflammatory bowel disease, 1996-2003. *Gastroenterology* 2007; **133**: 1779-1786 [PMID: 18054550 DOI: 10.1053/j.gastro.2007.09.022]

37 **Lichtenstein GR**, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, Langholff W, Londhe A, Sandborn WJ. 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**: 1409-1422 [PMID: 22890223 DOI: 10.1038/ajg.2012.218]

38 **Springfeld C**, Sauerbrei A, Filusch A, Konstandin M, Hartschuh W, Sauer P, Encke J, Stremmel W, Schnitzler P. Fatal varicella in an immunocompromised adult associated with a European genotype E2 variant of varicella zoster virus. *J Clin Virol* 2009; **44**: 70-73 [PMID: 19056312 DOI: 10.1016/j.jcv.2008.10.004]

39 **Biank VF**, Sheth MK, Talano J, Margolis D, Simpson P, Kugathasan S, Stephens M. Association of Crohn's disease, thiopurines, and primary epstein-barr virus infection with hemophagocytic lymphohistiocytosis. *J Pediatr* 2011; **159**: 808-812 [PMID: 21722918 DOI: 10.1016/j.jpeds.2011.04.045]

40 **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**: 306-308 [PMID: 24520429 DOI: 10.4240/wjgs.v5.i11.306]

41 **Pizzo PA**. Fever in immunocompromised patients. *N Engl J Med* 1999; **341**: 893-900 [PMID: 10486422 DOI: 10.1056/nejm199909163411207]

42 **Viget N**, Vernier-Massouille G, Salmon-Ceron D, Yazdanpanah Y, Colombel JF. Opportunistic infections in patients with inflammatory bowel disease: prevention and diagnosis. *Gut* 2008; **57**: 549-558 [PMID: 18178610 DOI: 10.1136/gut.2006.114660]

43 **Mylonaki M**, Langmead L, Pantes A, Johnson F, Rampton DS. Enteric infection in relapse of inflammatory bowel disease: importance of microbiological examination of stool. *Eur J Gastroenterol Hepatol* 2004; **16**: 775-778 [PMID: 15256979 DOI: 10.1097/01.meg.0000131040.38607.09]

44 **Chang LJ**, Hsiao CJ, Chen B, Liu TY, Ding J, Hsu WT, Su-Ortiz V, Chen ST, Su KY, Wu HP, Lee CC. Accuracy and comparison of two rapid multiplex PCR tests for gastroenteritis pathogens: a systematic review and meta-analysis. *BMJ Open Gastroenterol* 2021; **8** [PMID: 33648983 DOI: 10.1136/bmjgast-2020-000553]

45 **Langer-Gould A**, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med* 2005; **353**: 375-381 [PMID: 15947078 DOI: 10.1056/nejmoa051847]

46 **Kroger A**, Bahta L, Hunter P. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). CDC [Internet]. [cited 10 January 2021] Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html

47 **Dezfoli S**, Horton HA, Thepyasuwan N, Berel D, Targan SR, Vasiliauskas EA, Dubinsky M, Shih DQ, Kaur M, McGovern DP, Ippoliti A, Feldman EJ, Melmed GY. Combined Immunosuppression Impairs Immunogenicity to Tetanus and Pertussis Vaccination Among Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2015; **21**: 1754-1760 [PMID: 25985242 DOI: 10.1097/MIB.0000000000000448]

48 **Launay O**, Abitbol V, Krivine A, Slama LB, Bourreille A, Dupas JL, Hébuterne X, Savoye G, Deplanque D, Bouhnik Y, Pelletier AL, Galtier F, Laharie D, Nachury M, Zerbib F, Allez M, Bommelaer G, Duclos B, Lucht F, Gougeon ML, Tartour E, Rozenberg F, Hanslik T, Beaugerie L, Carrat F; MICIVAX Study Group. Immunogenicity and Safety of Influenza Vaccine in Inflammatory Bowel Disease Patients Treated or not with Immunomodulators and/or Biologics: A Two-year Prospective Study. *J Crohns Colitis* 2015; **9**: 1096-1107 [PMID: 26351392 DOI: 10.1093/ecco-jcc/jjv152]

49 **Rahier JF**. Management of IBD Patients with Current Immunosuppressive Therapy and Concurrent Infections. *Dig Dis* 2015; **33** Suppl 1: 50-56 [PMID: 26367373 DOI: 10.1159/000437066]

50 **Bell BP**, Shapiro CN, Alter MJ, Moyer LA, Judson FN, Mottram K, Fleenor M, Ryder PL, Margolis HS. The diverse patterns of hepatitis A epidemiology in the United States-implications for vaccination strategies. *J Infect Dis* 1998; **178**: 1579-1584 [PMID: 9815207 DOI: 10.1086/314518]

51 **Cuthbert JA**. Hepatitis A: old and new. *Clin Microbiol Rev* 2001; **14**: 38-58 [PMID: 11148002 DOI: 10.1128/CMR.14.1.38-58.2001]

52 **Farraye FA**, Melmed GY, Lichtenstein GR, Kane SV. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. *Am J Gastroenterol* 2017; **112**: 241-258 [PMID: 28071656 DOI: 10.1038/ajg.2016.537]

53 **Park SK**, Choi CH, Chun J, Lee H, Kim ES, Park JJ, Park CH, Lee BI, Jung Y, Park DI, Kim DY, Park H, Jeen YT; IBD Research Group of the Korean Association for the Study of Intestinal Diseases. Prevention and management of viral hepatitis in inflammatory bowel disease: a clinical practice guideline by the Korean Association for the Study of Intestinal Diseases. *Intest Res* 2020; **18**: 18-33 [PMID: 32013312 DOI: 10.5217/ir.2019.09155]

54 **Manser CN**, Maillard MH, Rogler G, Schreiner P, Rieder F, Bühler S; on behalf of Swiss IBDnet, an official working group of the Swiss Society of Gastroenterology. Vaccination in Patients with Inflammatory Bowel Diseases. *Digestion* 2020; **101** Suppl 1: 58-68 [PMID: 31968344 DOI: 10.1159/000503253]

55 **Bryan JP**, Henry CH, Hoffman AG, South-Paul JE, Smith JA, Cruess D, Spieker JM, de Medina M. Randomized, cross-over, controlled comparison of two inactivated hepatitis A vaccines. *Vaccine*

2000; **19**: 743-750 [PMID: 11115695 DOI: 10.1016/S0264-410X(00)00301-7]
56 **Park SH**, Yang SK, Park SK, Kim JW, Yang DH, Jung KW, Kim KJ, Ye BD, Byeon JS, Myung SJ, Kim JH. Efficacy of hepatitis A vaccination and factors impacting on seroconversion in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2014; **20**: 69-74 [PMID: 24284413 DOI: 10.1097/01.MIB.0000437736.91712.a1]
57 **Petruzziello A**, Marigliano S, Loquercio G, Cacciapuoti C. Hepatitis C virus (HCV) genotypes distribution: an epidemiological up-date in Europe. *Infect Agent Cancer* 2016; **11**: 53 [PMID: 27752280 DOI: 10.1186/s13027-016-0099-0]
58 **Losurdo G**, Iannone A, Contaldo A, Barone M, Ierardi E, Di Leo A, Principi M. Chronic Viral Hepatitis in a Cohort of Inflammatory Bowel Disease Patients from Southern Italy: A Case-Control Study. *Pathogens* 2020; **9** [PMID: 33113974 DOI: 10.3390/pathogens9110870]
59 **Papa A**, Felice C, Marzo M, Andrisani G, Armuzzi A, Covino M, Mocci G, Pugliese D, De Vitis I, Gasbarrini A, Rapaccini GL, Guidi L. Prevalence and natural history of hepatitis B and C infections in a large population of IBD patients treated with anti-tumor necrosis factor-α agents. *J Crohns Colitis* 2013; **7**: 113-119 [PMID: 22464811 DOI: 10.1016/j.crohns.2012.03.001]
60 **Huang ML**, Xu XT, Shen J, Qiao YQ, Dai ZH, Ran ZH. 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**: 282-287 [PMID: 24067604 DOI: 10.1016/j.crohns.2013.08.017]
61 **Loras C**, Saro C, Gonzalez-Huix F, Mínguez M, Merino O, Gisbert JP, Barrio J, Bernal A, Gutiérrez A, Piqueras M, Calvet X, Andreu M, Abad A, Ginard D, Bujanda L, Panés J, Torres M, Fernández-Bañares F, Viver JM, Esteve M; GETECCu (Grupo Español de Enfermedades de Crohn y Colitis Ulcerosa). Prevalence and factors related to hepatitis B and C in inflammatory bowel disease patients in Spain: a nationwide, multicenter study. *Am J Gastroenterol* 2009; **104**: 57-63 [PMID: 19098850 DOI: 10.1038/ajg.2008.4]
62 **Vermehren J**, Yu ML, Monto A, Yao JD, Anderson C, Bertuzis R, Schneider G, Sarrazin C. Multi-center evaluation of the Abbott RealTime HCV assay for monitoring patients undergoing antiviral therapy for chronic hepatitis C. *J Clin Virol* 2011; **52**: 133-137 [PMID: 21803650 DOI: 10.1016/j.jcv.2011.07.007]
63 **Chapko MK**, Dufour DR, Hatia RI, Drobeniuc J, Ward JW, Teo CG. Cost-effectiveness of strategies for testing current hepatitis C virus infection. *Hepatology* 2015; **62**: 1396-1404 [PMID: 26126725 DOI: 10.1002/hep.27966]
64 **European Association for the Study of the Liver**. EASL Recommendations on Treatment of Hepatitis C 2018. *J Hepatol* 2018; **69**: 461-511 [PMID: 29650333 DOI: 10.1016/j.jhep.2018.03.026]
65 **Degasperi E**, Caprioli F, El Sherif O, Back D, Colombo M, Aghemo A. Challenges in treating patients with inflammatory bowel disease and concurrent viral hepatitis infection. *Expert Rev Gastroenterol Hepatol* 2016; **10**: 1373-1383 [PMID: 27718758 DOI: 10.1080/17474124.2016.1246181]
66 **Brunasso AM**, Puntoni M, Gulia A, Massone C. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. *Rheumatology (Oxford)* 2011; **50**: 1700-1711 [PMID: 21690185 DOI: 10.1093/rheumatology/ker190]
67 **Viganò M**, Degasperi E, Aghemo A, Lampertico P, Colombo M. Anti-TNF drugs in patients with hepatitis B or C virus infection: safety and clinical management. *Expert Opin Biol Ther* 2012; **12**: 193-207 [PMID: 22188392 DOI: 10.1517/14712598.2012.646986]
68 **Ott JJ**, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 2012; **30**: 2212-2219 [PMID: 22273662 DOI: 10.1016/j.vaccine.2011.12.116]
69 **Schweitzer A**, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; **386**: 1546-1555 [PMID: 26231459 DOI: 10.1016/S0140-6736(15)61412-X]
70 **Chevaux JB**, Nani A, Oussalah A, Venard V, Bensenane M, Belle A, Gueant JL, Bigard MA, Bronowicki JP, Peyrin-Biroulet L. Prevalence of hepatitis B and C and risk factors for nonvaccination in inflammatory bowel disease patients in Northeast France. *Inflamm Bowel Dis* 2010; **16**: 916-924 [PMID: 19885908 DOI: 10.1002/ibd.21147]
71 **Gandhi RT**, Wurcel A, Lee H, McGovern B, Boczanowski M, Gerwin R, Corcoran CP, Szczepiorkowski Z, Toner S, Cohen DE, Sax PE, Ukomadu C. Isolated antibody to hepatitis B core antigen in human immunodeficiency virus type-1-infected individuals. *Clin Infect Dis* 2003; **36**: 1602-1605 [PMID: 12802762 DOI: 10.1086/375084]
72 **Jiang HY**, Wang SY, Deng M, Li YC, Ling ZX, Shao L, Ruan B. Immune response to hepatitis B vaccination among people with inflammatory bowel diseases: A systematic review and meta-analysis. *Vaccine* 2017; **35**: 2633-2641 [PMID: 28404358 DOI: 10.1016/j.vaccine.2017.03.080]
73 **Kochhar GS**, Mohan BP, Khan SR, Chandan S, Kassab LL, Ponnada S, Desai A, Caldera F, Dulai PS, Farraye F. Hepatitis-B Vaccine Response in Inflammatory Bowel Disease Patients: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis* 2021; Online ahead of print [PMID: 33393585 DOI: 10.1093/ibd/izaa353]
74 **Gisbert JP**, Menchén L, García-Sánchez V, Marín I, Villagrasa JR, Chaparro M. Comparison of the effectiveness of two protocols for vaccination (standard and double dosage) against hepatitis B virus in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2012; **35**: 1379-1385 [PMID: 22530631 DOI: 10.1111/j.1365-2036.2012.05110.x]
75 **Gisbert JP**, Villagrasa JR, Rodríguez-Nogueiras A, Chaparro M. Efficacy of hepatitis B vaccination

and revaccination and factors impacting on response in patients with inflammatory bowel disease. *Am J Gastroenterol* 2012; **107**: 1460-1466 [PMID: 23034605 DOI: 10.1038/ajg.2012.79]

76 **WHO Publication**. Hepatitis B vaccines: WHO position paper--recommendations. *Vaccine* 2010; **28**: 589-590 [PMID: 19896455 DOI: 10.1016/j.vaccine.2009.10.110]

77 **Moses J**, Alkhouri N, Shannon A, Raig K, Lopez R, Danziger-Isakov L, Feldstein AE, Zein NN, Wyllie R, Carter-Kent C. Hepatitis B immunity and response to booster vaccination in children with inflammatory bowel disease treated with infliximab. *Am J Gastroenterol* 2012; **107**: 133-138 [PMID: 21876562 DOI: 10.1038/ajg.2011.295]

78 **Loomba R**, Liang TJ. Hepatitis B Reactivation Associated With Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions. *Gastroenterology* 2017; **152**: 1297-1309 [PMID: 28219691 DOI: 10.1053/j.gastro.2017.02.009]

79 **Loras C**, Gisbert JP, Mínguez M, Merino O, Bujanda L, Saro C, Domenech E, Barrio J, Andreu M, Ordás I, Vida L, Bastida G, González-Huix F, Piqueras M, Ginard D, Calvet X, Gutiérrez A, Abad A, Torres M, Panés J, Chaparro M, Pascual I, Rodriguez-Carballeira M, Fernández-Bañares F, Viver JM, Esteve M; REPENTINA study; GETECCU (Grupo Español de Enfermedades de Crohn y Colitis Ulcerosa) Group. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. *Gut* 2010; **59**: 1340-1346 [PMID: 20577000 DOI: 10.1136/gut.2010.208413]

80 **Park SH**, Yang SK, Lim YS, Shim JH, Yang DH, Jung KW, Kim KJ, Ye BD, Byeon JS, Myung SJ, Kim JH. Clinical courses of chronic hepatitis B virus infection and inflammatory bowel disease in patients with both diseases. *Inflamm Bowel Dis* 2012; **18**: 2004-2010 [PMID: 22337144 DOI: 10.1002/ibd.22905]

81 **Lan JL**, Chen YM, Hsieh TY, Chen YH, Hsieh CW, Chen DY, Yang SS. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. *Ann Rheum Dis* 2011; **70**: 1719-1725 [PMID: 21719446 DOI: 10.1136/ard.2010.148783]

82 **Pauly MP**, Tucker LY, Szpakowski JL, Ready JB, Baer D, Hwang J, Lok AS. Incidence of Hepatitis B Virus Reactivation and Hepatotoxicity in Patients Receiving Long-term Treatment With Tumor Necrosis Factor Antagonists. *Clin Gastroenterol Hepatol* 2018; **16**: 1964-1973. e1 [PMID: 29702293 DOI: 10.1016/j.cgh.2018.04.033]

83 **Madonia S**, Orlando A, Scimeca D, Olivo M, Rossi F, Cottone M. Occult hepatitis B and infliximab-induced HBV reactivation. *Inflamm Bowel Dis* 2007; **13**: 508-509 [PMID: 17206687 DOI: 10.1002/ibd.20035]

84 **Lee YH**, Bae SC, Song GG. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. *Int J Rheum Dis* 2013; **16**: 527-531 [PMID: 24164839 DOI: 10.1111/1756-185X.12154]

85 **Reddy KR**, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT; American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148**: 215-9; quiz e16 [PMID: 25447850 DOI: 10.1053/j.gastro.2014.10.039]

86 **Muñoz N**, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, Snijders PJ, Meijer CJ; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003; **348**: 518-527 [PMID: 12571259 DOI: 10.1056/nejmoa021641]

87 **Handisurya A**, Lázár S, Papay P, Primas C, Haitel A, Horvat R, Tanew A, Vogelsang H, Kirnbauer R. Anogenital Human Papillomavirus Prevalence is Unaffected by Therapeutic Tumour Necrosis Factor-alpha Inhibition. *Acta Derm Venereol* 2016; **96**: 494-498 [PMID: 26581127 DOI: 10.2340/00015555-2298]

88 **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**: 451-458 [PMID: 18996382 DOI: 10.1053/j.gastro.2008.10.021]

89 **Lees CW**, Critchley J, Chee N, Beez T, Gailer RE, Williams AR, Shand AG, Arnott ID, Satsangi J. Lack of association between cervical dysplasia and IBD: a large case-control study. *Inflamm Bowel Dis* 2009; **15**: 1621-1629 [PMID: 19618462 DOI: 10.1002/ibd.20959]

90 **Hazenberg HMJL**, de Boer NKH, Mulder CJJ, Mom SH, van Bodegraven AA, Tack Md PhD GJ. Neoplasia and Precursor Lesions of the Female Genital Tract in IBD: Epidemiology, Role of Immunosuppressants, and Clinical Implications. *Inflamm Bowel Dis* 2018; **24**: 510-531 [PMID: 29462389 DOI: 10.1093/ibd/izx062]

91 **Jacobson DL**, Bousvaros A, Ashworth L, Carey R, Shrier LA, Burchett SK, Renna H, Lu Y. Immunogenicity and tolerability to human papillomavirus-like particle vaccine in girls and young women with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 1441-1449 [PMID: 23567780 DOI: 10.1097/MIB.0b013e318281341b]

92 **Rungoe C**, Simonsen J, Riis L, Frisch M, Langholz E, Jess T. Inflammatory bowel disease and cervical neoplasia: a population-based nationwide cohort study. *Clin Gastroenterol Hepatol* 2015; **13**: 693-700. e1 [PMID: 25086189 DOI: 10.1016/j.cgh.2014.07.036]

93 **Waszczuk E**, Waszczuk K, Bohdanowicz-Pawlak A, Florjański J. Women with inflammatory bowel diseases have a suboptimal cervical cancer screening rate and are not aware of the recommended human papilloma virus vaccine. *Gynecol Endocrinol* 2018; **34**: 656-658 [PMID: 29475388 DOI: 10.1080/09513590.2017.1416466]

94 **Walsh AJ**, Weltman M, Burger D, Vivekanandarajah S, Connor S, Howlett M, Radford-Smith G, Selby W, Veillard AS, Grimm MC, Travis SP, Lawrance IC. Implementing guidelines on the prevention of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2013; **7**: e449-e456 [PMID: 23601754 DOI: 10.1016/j.crohns.2013.02.019]

95 **Stobaugh DJ**, Deepak P, Ehrenpreis ED. Hospitalizations for vaccine preventable pneumonias in patients with inflammatory bowel disease: a 6-year analysis of the Nationwide Inpatient Sample. *Clin Exp Gastroenterol* 2013; **6**: 43-49 [PMID: 23818801 DOI: 10.2147/CEG.S42514]

96 **Tinsley A**, Navabi S, Williams ED, Liu G, Kong L, Coates MD, Clarke K. Increased Risk of Influenza and Influenza-Related Complications Among 140,480 Patients With Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2019; **25**: 369-376 [PMID: 30020478 DOI: 10.1093/ibd/izy243]

97 **Uyeki TM**, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, Gravenstein S, Hayden FG, Harper SA, Hirshon JM, Ison MG, Johnston BL, Knight SL, McGeer A, Riley LE, Wolfe CR, Alexander PE, Pavia AT. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. *Clin Infect Dis* 2019; **68**: 895-902 [PMID: 30834445 DOI: 10.1093/cid/ciy874]

98 **Andrisani G**, Frasca D, Romero M, Armuzzi A, Felice C, Marzo M, Pugliese D, Papa A, Mocci G, De Vitis I, Rapaccini GL, Blomberg BB, Guidi L. 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**: 301-307 [PMID: 22673636 DOI: 10.1016/j.crohns.2012.05.011]

99 **Hagihara Y**, Ohfuji S, Watanabe K, Yamagami H, Fukushima W, Maeda K, Kamata N, Sogawa M, Shiba M, Tanigawa T, Tominaga K, Watanabe T, Fujiwara Y, Hirota Y, Arakawa T. Infliximab and/or immunomodulators inhibit immune responses to trivalent influenza vaccination in adults with inflammatory bowel disease. *J Crohns Colitis* 2014; **8**: 223-233 [PMID: 24011513 DOI: 10.1016/j.crohns.2013.08.008]

100 **Caldera F**, Hillman L, Saha S, Wald A, Grimes I, Zhang Y, Sharpe AR, Reichelderfer M, Hayney MS. 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 [PMID: 31504526 DOI: 10.1093/ibd/izz164]

101 **Saag MS**, Gandhi RT, Hoy JF, Landovitz RJ, Thompson MA, Sax PE, Smith DM, Benson CA, Buchbinder SP, Del Rio C, Eron JJ Jr, Fätkenheuer G, Günthard HF, Molina JM, Jacobsen DM, Volberding PA. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society-USA Panel. *JAMA* 2020; **324**: 1651-1669 [PMID: 33052386 DOI: 10.1001/jama.2020.17025]

102 **Skamnelos A**, Tatsioni A, Katsanos KH, Tsianos V, Christodoulou D, Tsianos EV. CD4 count remission hypothesis in patients with inflammatory bowel disease and human immunodeficiency virus infection: a systematic review of the literature. *Ann Gastroenterol* 2015; **28**: 337-346 [PMID: 26126511]

103 **Guillo L**, Uzzan M, Beaugerie L, Gornet JM, Amiot A, Pelletier AL, Altwegg R, Laharie D, Abitbol V, Filippi J, Goutorbe F, Nachury M, Nancey S, Viennot S, Reenaers C, Amil M, Caillo L, Buisson A, Collins M, Picon L, Vidon M, Benezech A, Rabaud C, Baumann C, Rousseau H, Dubourg G, Serrero M, Peyrin-Biroulet L. Impact of HIV Infection on the Course of Inflammatory Bowel Disease and Drug Safety Profile: A Multicenter GETAID Study. *Clin Gastroenterol Hepatol* 2020; Online ahead of print [PMID: 33359726 DOI: 10.1016/j.cgh.2020.12.023]

104 **Viazis N**, Vlachogiannakos J, Georgiou O, Rodias M, Georgiadis D, Papastamopoulos V, Baraboutis IG, Karamanolis DG, Skoutelis A. Course of inflammatory bowel disease in patients infected with human immunodeficiency virus. *Inflamm Bowel Dis* 2010; **16**: 507-511 [PMID: 19714759 DOI: 10.1002/ibd.21077]

105 **Dikman AE**, Schonfeld E, Srisarajivakul NC, Poles MA. Human Immunodeficiency Virus-Associated Diarrhea: Still an Issue in the Era of Antiretroviral Therapy. *Dig Dis Sci* 2015; **60**: 2236-2245 [PMID: 25772777 DOI: 10.1007/s10620-015-3615-y]

106 **Mentec H**, Leport C, Leport J, Marche C, Harzic M, Vildé JL. Cytomegalovirus colitis in HIV-1-infected patients: a prospective research in 55 patients. *AIDS* 1994; **8**: 461-467 [PMID: 8011249 DOI: 10.1097/00002030-199404000-00007]

107 **Chamberlain RS**, Atkins S, Saini N, White JC. Ileal perforation caused by cytomegalovirus infection in a critically ill adult. *J Clin Gastroenterol* 2000; **30**: 432-435 [PMID: 10875475 DOI: 10.1097/00004836-200006000-00016]

108 **von Both U**, Laffer R, Grube C, Bossart W, Gaspert A, Günthard HF. Acute cytomegalovirus colitis presenting during primary HIV infection: an unusual case of an immune reconstitution inflammatory syndrome. *Clin Infect Dis* 2008; **46**: e38-e40 [PMID: 18199043 DOI: 10.1086/526783]

109 **Danzig JB**, Brandt LJ, Reinus JF, Klein RS. Gastrointestinal malignancy in patients with AIDS. *Am J Gastroenterol* 1991; **86**: 715-718 [PMID: 2038993]

110 **Braga Neto MB**, Aguiar CV, Maciel JG, Oliveira BM, Sevilleja JE, Oriá RB, Brito GA, Warren CA, Guerrant RL, Lima AA. Evaluation of HIV protease and nucleoside reverse transcriptase inhibitors on proliferation, necrosis, apoptosis in intestinal epithelial cells and electrolyte and water transport and epithelial barrier function in mice. *BMC Gastroenterol* 2010; **10**: 90 [PMID: 20701796 DOI: 10.1186/1471-230X-10-90]

111 **Wu X**, Sun L, Zha W, Studer E, Gurley E, Chen L, Wang X, Hylemon PB, Pandak WM Jr, Sanyal

AJ, Zhang L, Wang G, Chen J, Wang JY, Zhou H. HIV protease inhibitors induce endoplasmic reticulum stress and disrupt barrier integrity in intestinal epithelial cells. *Gastroenterology* 2010; **138**: 197-209 [PMID: 19732776 DOI: 10.1053/j.gastro.2009.08.054]

112 **Cello JP**, Day LW. Idiopathic AIDS enteropathy and treatment of gastrointestinal opportunistic pathogens. *Gastroenterology* 2009; **136**: 1952-1965 [PMID: 19457421 DOI: 10.1053/j.gastro.2008.12.073]

113 **Calabrese LH**, Zein N, Vassilopoulos D. Safety of antitumour necrosis factor (anti-TNF) therapy in patients with chronic viral infections: hepatitis C, hepatitis B, and HIV infection. *Ann Rheum Dis* 2004; **63** Suppl 2: ii18-ii24 [PMID: 15479865 DOI: 10.1136/ard.2004.028209]

114 **Wangsiricharoen S**, Ligon C, Gedmintas L, Dehrab A, Tungsiripat M, Bingham C 3rd, Lozada C, Calabrese L. Rates of Serious Infections in HIV-Infected Patients Receiving Tumor Necrosis Factor Inhibitor Therapy for Concomitant Autoimmune Diseases. *Arthritis Care Res (Hoboken)* 2017; **69**: 449-452 [PMID: 27332039 DOI: 10.1002/acr.22955]

115 **Habib SF**, Hasan MZ, Salam I. Infliximab therapy for HIV positive Crohn's disease: A case report. *J Crohns Colitis* 2009; **3**: 302-304 [PMID: 21172291 DOI: 10.1016/j.crohns.2009.06.002]

116 **Workowski KA**, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 2015; **64**: 1-137 [PMID: 26042815 DOI: 10.1097/00019048-200206000-00012]

117 **Steiner I**, Benninger F. Manifestations of Herpes Virus Infections in the Nervous System. *Neurol Clin* 2018; **36**: 725-738 [PMID: 30366551 DOI: 10.1016/j.ncl.2018.06.005]

118 **Pinna AD**, Rakela J, Demetris AJ, Fung JJ. Five cases of fulminant hepatitis due to herpes simplex virus in adults. *Dig Dis Sci* 2002; **47**: 750-754 [PMID: 11991604 DOI: 10.1023/A:1014779614525]

119 **Afessa B**. Mycobacterial and nonbacterial pulmonary complications in hospitalized patients with human immunodeficiency virus infection: a prospective, cohort study. *BMC Pulm Med* 2001; **1**: 1 [PMID: 11602023 DOI: 10.1186/1471-2466-1-1]

120 **Byers RJ**, Hasleton PS, Quigley A, Dennett C, Klapper PE, Cleator GM, Faragher EB. Pulmonary herpes simplex in burns patients. *Eur Respir J* 1996; **9**: 2313-2317 [PMID: 8947077 DOI: 10.1183/09031936.96.09112313]

121 **Ramanathan J**, Rammouni M, Baran J Jr, Khatib R. Herpes simplex virus esophagitis in the immunocompetent host: an overview. *Am J Gastroenterol* 2000; **95**: 2171-2176 [PMID: 11007213 DOI: 10.1111/j.1572-0241.2000.02299.x]

122 **Lee B**, Caddy G. A rare cause of dysphagia: herpes simplex esophagitis. *World J Gastroenterol* 2007; **13**: 2756-2757 [PMID: 17569149 DOI: 10.3748/wjg.v13.i19.2756]

123 **Canalejo E**, García Durán F, Cabello N, García Martínez J. Herpes esophagitis in healthy adults and adolescents: report of 3 cases and review of the literature. *Medicine (Baltimore)* 2010; **89**: 204-210 [PMID: 20616659 DOI: 10.1097/MD.0b013e3181e949ed]

124 **Klausner JD**, Kohn R, Kent C. Etiology of clinical proctitis among men who have sex with men. *Clin Infect Dis* 2004; **38**: 300-302 [PMID: 14699467 DOI: 10.1086/380838]

125 **Sigle GW**, Kim R. Sexually transmitted proctitis. *Clin Colon Rectal Surg* 2015; **28**: 70-78 [PMID: 26034402 DOI: 10.1055/s-0035-1547334]

126 **Sandgren KE**, Price NB, Bishop WP, McCarthy PJ. Herpes Simplex Proctitis Mimicking Inflammatory Bowel Disease in a Teenaged Male. *Case Rep Pediatr* 2017; **2017**: 3547230 [PMID: 28473937 DOI: 10.1155/2017/3547230]

127 **Santos-Antunes J**, Abreu C, Magro F, Coelho R, Vilas-Boas F, Andrade P, Lopes S, Macedo G. Disseminated cutaneous herpes simplex infection in a patient with Crohn's disease under azathioprine and steroids: First case report and literature review. *J Crohns Colitis* 2014; **8**: 326-330 [PMID: 24257435 DOI: 10.1016/j.crohns.2013.10.011]

128 **el-Serag HB**, Zwas FR, Cirillo NW, Eisen RN. Fulminant herpes colitis in a patient with Crohn's disease. *J Clin Gastroenterol* 1996; **22**: 220-223 [PMID: 8724263 DOI: 10.1097/00004836-199604000-00015]

129 **Schunter MO**, Walles T, Fritz P, Meyding-Lamadé U, Thon KP, Fellermann K, Stange EF, Lamadé W. Herpes simplex virus colitis complicating ulcerative colitis: A case report and brief review on superinfections. *J Crohns Colitis* 2007; **1**: 41-46 [PMID: 21172183 DOI: 10.1016/j.crohns.2007.06.004]

130 **Chevaux JB**, Peyrin-Biroulet L. Herpes simplex virus colitis complicating the course of a patient with Crohn's disease and cirrhosis: an underestimated association? *Gastroenterol Hepatol (N Y)* 2010; **6**: 122-124 [PMID: 20567556]

131 **Jafri H**, Kalina DR, Aziz T, Serrano PE, Haider S. Herpes Simplex Virus Colitis in a Patient with Newly Diagnosed Crohn's Disease. *Case Rep Med* 2018; **2018**: 7591709 [PMID: 30013599 DOI: 10.1155/2018/7591709]

132 **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**: 1179547619858979 [PMID: 31320810 DOI: 10.1177/1179547619858979]

133 **Zuhair M**, Smit GSA, Wallis G, Jabbar F, Smith C, Devleesschauwer B, Griffiths P. Estimation of the worldwide seroprevalence of cytomegalovirus: A systematic review and meta-analysis. *Rev Med Virol* 2019; **29**: e2034 [PMID: 30706584 DOI: 10.1002/rmv.2034]

134 **You DM**, Johnson MD. Cytomegalovirus infection and the gastrointestinal tract. *Curr Gastroenterol Rep* 2012; **14**: 334-342 [PMID: 22588614 DOI: 10.1007/s11894-012-0266-4]

135 **Lv YL**, Han FF, Jia YJ, Wan ZR, Gong LL, Liu H, Liu LH. Is cytomegalovirus infection related to

inflammatory bowel disease, especially steroid-resistant inflammatory bowel disease? *Infect Drug Resist* 2017; **10**: 511-519 [PMID: 29276397 DOI: 10.2147/IDR.S149784]

136 **Domènech E**, Vega R, Ojanguren I, Hernández A, Garcia-Planella E, Bernal I, Rosinach M, Boix J, Cabré E, Gassull MA. Cytomegalovirus infection in ulcerative colitis: a prospective, comparative study on prevalence and diagnostic strategy. *Inflamm Bowel Dis* 2008; **14**: 1373-1379 [PMID: 18452205 DOI: 10.1002/ibd.20498]

137 **Dimitroulia E**, Spanakis N, Konstantinidou AE, Legakis NJ, Tsakris A. Frequent detection of cytomegalovirus in the intestine of patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2006; **12**: 879-884 [PMID: 16954807 DOI: 10.1097/01.mib.0000231576.11678.57]

138 **Lopes S**, Andrade P, Conde S, Liberal R, Dias CC, Fernandes S, Pinheiro J, Simões JS, Carneiro F, Magro F, Macedo G. Looking into Enteric Virome in Patients with IBD: Defining Guilty or Innocence? *Inflamm Bowel Dis* 2017; **23**: 1278-1284 [PMID: 28617757 DOI: 10.1097/MIB.0000000000001167]

139 **Römkens TE**, Bulte GJ, Nissen LH, Drenth JP. Cytomegalovirus in inflammatory bowel disease: A systematic review. *World J Gastroenterol* 2016; **22**: 1321-1330 [PMID: 26811669 DOI: 10.3748/wjg.v22.i3.1321]

140 **Kishore J**, Ghoshal U, Ghoshal UC, Krishnani N, Kumar S, Singh M, Ayyagari A. Infection with cytomegalovirus in patients with inflammatory bowel disease: prevalence, clinical significance and outcome. *J Med Microbiol* 2004; **53**: 1155-1160 [PMID: 15496396 DOI: 10.1099/jmm.0.45629-0]

141 **Yi F**, Zhao J, Luckheeram RV, Lei Y, Wang C, Huang S, Song L, Wang W, Xia B. The prevalence and risk factors of cytomegalovirus infection in inflammatory bowel disease in Wuhan, Central China. *Virol J* 2013; **10**: 43 [PMID: 23374225 DOI: 10.1186/1743-422X-10-43]

142 **Weng MT**, Tung CC, Lee YS, Leong YL, Shieh MJ, Shun CT, Wang CY, Wong JM, Wei SC. Cytomegalovirus colitis in hospitalized inflammatory bowel disease patients in Taiwan: a referral center study. *BMC Gastroenterol* 2017; **17**: 28 [PMID: 28193173 DOI: 10.1186/s12876-017-0586-9]

143 **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 [PMID: 27875356 DOI: 10.1097/MCG.0000000000000758]

144 **Gauss A**, Rosenstiel S, Schnitzler P, Hinz U, Rehlen T, Kadmon M, Ehehalt R, Stremmel W, Zawierucha A. Intestinal cytomegalovirus infection in patients hospitalized for exacerbation of inflammatory bowel disease: a 10-year tertiary referral center experience. *Eur J Gastroenterol Hepatol* 2015; **27**: 712-720 [PMID: 25919654 DOI: 10.1097/MEG.0000000000000361]

145 **Lavagna A**, Bergallo M, Daperno M, Sostegni R, Costa C, Leto R, Crocellà L, Molinaro G, Rocca R, Cavallo R, Pera A. Infliximab and the risk of latent viruses reactivation in active Crohn's disease. *Inflamm Bowel Dis* 2007; **13**: 896-902 [PMID: 17345605 DOI: 10.1002/ibd.20131]

146 **Nakase H**, Chiba T. TNF-alpha is an important pathogenic factor contributing to reactivation of cytomegalovirus in inflamed mucosa of colon in patients with ulcerative colitis: lesson from clinical experience. *Inflamm Bowel Dis* 2010; **16**: 550-551 [PMID: 19637380 DOI: 10.1002/ibd.21047]

147 **Pillet S**, Jarlot C, Courault M, Del Tedesco E, Chardon R, Saint-Sardos P, Presles E, Phelip JM, Berthelot P, Pozzetto B, Roblin X. Infliximab Does Not Worsen Outcomes During Flare-ups Associated with Cytomegalovirus Infection in Patients with Ulcerative Colitis. *Inflamm Bowel Dis* 2015; **21**: 1580-1586 [PMID: 25933392 DOI: 10.1097/MIB.0000000000000412]

148 **Nowacki TM**, Bettenworth D, Meister T, Heidemann J, Lenze F, Schmidt HH, Heinzow HS. Novel score predicts risk for cytomegalovirus infection in ulcerative colitis. *J Clin Virol* 2018; **105**: 103-108 [PMID: 29940421 DOI: 10.1016/j.jcv.2018.06.002]

149 **Nguyen M**, Bradford K, Zhang X, Shih DQ. Cytomegalovirus Reactivation in Ulcerative Colitis Patients. *Ulcers* 2011; **2011** [PMID: 21731826 DOI: 10.1155/2011/282507]

150 **Schenk W**, Klugmann T, Borkenhagen A, Klecker C, Dietel P, Kirschner R, Schneider E, Bruns T, Stallmach A, Teich N. 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 [PMID: 30506156 DOI: 10.1007/s00384-018-3210-8]

151 **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**: 1539-1546 [PMID: 29718356 DOI: 10.1093/ibd/izy045]

152 **Mourad FH**, Hashash JG, Kariyawasam VC, Leong RW. Ulcerative Colitis and Cytomegalovirus Infection: From A to Z. *J Crohns Colitis* 2020; **14**: 1162-1171 [PMID: 32103246 DOI: 10.1093/ecco-jcc/jjaa036]

153 **Lamb CA**, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H; IBD guidelines eDelphi consensus group, Gaya DR, Iqbal TH, Taylor SA, Smith M, Brookes M, Hansen R, Hawthorne AB. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019; **68**: s1-s106 [PMID: 31562236 DOI: 10.1136/gutjnl-2019-318484]

154 **Durand CM**, Marr KA, Arnold CA, Tang L, Durand DJ, Avery RK, Valsamakis A, Neofytos D. Detection of cytomegalovirus DNA in plasma as an adjunct diagnostic for gastrointestinal tract disease in kidney and liver transplant recipients. *Clin Infect Dis* 2013; **57**: 1550-1559 [PMID:

23956167 DOI: 10.1093/cid/cit521]
155 **Maconi G**, Lombardini M, Furfaro F, Bezzio C, Zerbi P, Ardizzone S. Long-term outcome of inflammatory bowel diseases with cytomegalovirus colitis: effect of antiviral treatment. *Eur J Gastroenterol Hepatol* 2014; **26**: 1146-1151 [PMID: 25089547 DOI: 10.1097/MEG.0000000000000175]
156 **Pillet S**, Pozzetto B, Roblin X. Cytomegalovirus and ulcerative colitis: Place of antiviral therapy. *World J Gastroenterol* 2016; **22**: 2030-2045 [PMID: 26877608 DOI: 10.3748/wjg.v22.i6.2030]
157 **Heininger U**, Seward JF. Varicella. *Lancet* 2006; **368**: 1365-1376 [PMID: 17046469 DOI: 10.1016/S0140-6736(06)69561-5]
158 **Kopylov U**, Levin A, Mendelson E, Dovrat S, Book M, Eliakim R, Ben-Horin S. Prior varicella zoster virus exposure in IBD patients treated by anti-TNFs and other immunomodulators: implications for serological testing and vaccination guidelines. *Aliment Pharmacol Ther* 2012; **36**: 145-150 [PMID: 22612376 DOI: 10.1111/j.1365-2036.2012.05150.x]
159 **García-Doval I**, Pérez-Zafrilla B, Descalzo MA, Roselló R, Hernández MV, Gómez-Reino JJ, Carmona L; BIOBADASER 2. 0 Study Group. Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists. *Ann Rheum Dis* 2010; **69**: 1751-1755 [PMID: 20551153 DOI: 10.1136/ard.2009.125658]
160 **Cullen G**, Baden RP, Cheifetz AS. Varicella zoster virus infection in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18**: 2392-2403 [PMID: 22434654 DOI: 10.1002/ibd.22950]
161 **Schreiner P**, Mueller NJ, Fehr J, Maillard MH, Brand S, Michetti P, Schoepfer A, Restellini S, Vulliemoz M, Vavricka SR, Juillerat P, Rogler G, Biedermann L. Varicella zoster virus in inflammatory bowel disease patients: what every gastroenterologist should know. *J Crohns Colitis* 2020; Online ahead of print [PMID: 32592587 DOI: 10.1093/ecco-jcc/jjaa132]
162 **Schmutzhard J**, Merete Riedel H, Zweygberg Wirgart B, Grillner L. Detection of herpes simplex virus type 1, herpes simplex virus type 2 and varicella-zoster virus in skin lesions. Comparison of real-time PCR, nested PCR and virus isolation. *J Clin Virol* 2004; **29**: 120-126 [PMID: 14747031 DOI: 10.1016/S1386-6532(03)00113-6]
163 **Levin MJ**, Duchon JM, Swamy GK, Gershon AA. Varicella zoster immune globulin (VARIZIG) administration up to 10 days after varicella exposure in pregnant women, immunocompromised participants, and infants: Varicella outcomes and safety results from a large, open-label, expanded-access program. *PLoS One* 2019; **14**: e0217749 [PMID: 31269033 DOI: 10.1371/journal.pone.0217749]
164 **Gilden D**, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol* 2009; **8**: 731-740 [PMID: 19608099 DOI: 10.1016/S1474-4422(09)70134-6]
165 **Gilden D**, Nagel MA, Cohrs RJ, Mahalingam R. The variegate neurological manifestations of varicella zoster virus infection. *Curr Neurol Neurosci Rep* 2013; **13**: 374 [PMID: 23884722 DOI: 10.1007/s11910-013-0374-z]
166 **Chang K**, Lee HS, Kim YJ, Kim SO, Kim SH, Lee SH, Song EM, Hwang SW, Park SH, Yang DH, Ye BD, Byeon JS, Myung SJ, Yang SK. Increased Risk of Herpes Zoster Infection in Patients With Inflammatory Bowel Diseases in Korea. *Clin Gastroenterol Hepatol* 2018; **16**: 1928-1936. e2 [PMID: 29857150 DOI: 10.1016/j.cgh.2018.05.024]
167 **Winthrop KL**, Melmed GY, Vermeire S, Long MD, Chan G, Pedersen RD, Lawendy N, Thorpe AJ, Nduaka CI, Su C. Herpes Zoster Infection in Patients With Ulcerative Colitis Receiving Tofacitinib. *Inflamm Bowel Dis* 2018; **24**: 2258-2265 [PMID: 29850873 DOI: 10.1093/ibd/izy131]
168 **Sandborn WJ**, Panés J, D'Haens GR, Sands BE, Su C, Moscariello M, Jones T, Pedersen R, Friedman GS, Lawendy N, Chan G. Safety of Tofacitinib for Treatment of Ulcerative Colitis, Based on 4.4 Years of Data From Global Clinical Trials. *Clin Gastroenterol Hepatol* 2019; **17**: 1541-1550 [PMID: 30476584 DOI: 10.1016/j.cgh.2018.11.035]
169 **Lal H**, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, Levin MJ, McElhaney JE, Poder A, Puig-Barberà J, Vesikari T, Watanabe D, Weckx L, Zahaf T, Heineman TC; ZOE-50 Study Group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med* 2015; **372**: 2087-2096 [PMID: 25916341 DOI: 10.1056/NEJMoa1501184]
170 **Dooling KL**, Guo A, Patel M, Lee GM, Moore K, Belongia EA, Harpaz R. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. *MMWR Morb Mortal Wkly Rep* 2018; **67**: 103-108 [PMID: 29370152 DOI: 10.15585/mmwr.mm6703a5]
171 **Mok CC**. Herpes zoster vaccination in systemic lupus erythematosus: the current status. *Hum Vaccin Immunother* 2019; **15**: 45-48 [PMID: 30130445 DOI: 10.1080/21645515.2018.1514228]
172 **Vink P**, Delgado Mingorance I, Maximiano Alonso C, Rubio-Viqueira B, Jung KH, Rodriguez Moreno JF, Grande E, Marrupe Gonzalez D, Lowndes S, Puente J, Kristeleit H, Farrugia D, McNeil SA, Campora L, Di Paolo E, El Idrissi M, Godeaux O, López-Fauqued M, Salaun B, Heineman TC, Oostvogels L; Zoster-028 Study Group. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in patients with solid tumors, vaccinated before or during chemotherapy: A randomized trial. *Cancer* 2019; **125**: 1301-1312 [PMID: 30707761 DOI: 10.1002/cncr.31909]
173 **Dagnew AF**, Ilhan O, Lee WS, Woszczyk D, Kwak JY, Bowcock S, Sohn SK, Rodriguez Macías G, Chiou TJ, Quiel D, Aoun M, Navarro Matilla MB, de la Serna J, Milliken S, Murphy J, McNeil SA, Salaun B, Di Paolo E, Campora L, López-Fauqued M, El Idrissi M, Schuind A, Heineman TC, Van den Steen P, Oostvogels L; Zoster-039 study group. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised,

clinical trial and post-hoc efficacy analysis. *Lancet Infect Dis* 2019; **19**: 988-1000 [PMID: 31399377 DOI: 10.1016/S1473-3099(19)30163-X]

174 **Dunmire SK**, Verghese PS, Balfour HH Jr. Primary Epstein-Barr virus infection. *J Clin Virol* 2018; **102**: 84-92 [PMID: 29525635 DOI: 10.1016/j.jcv.2018.03.001]

175 **Andersson-Anvret M**, Forsby N, Klein G, Henle W. Relationship between the Epstein-Barr virus and undifferentiated nasopharyngeal carcinoma: correlated nucleic acid hybridization and histopathological examination. *Int J Cancer* 1977; **20**: 486-494 [PMID: 199543 DOI: 10.1002/ijc.2910200403]

176 **Thorley-Lawson DA**, Gross A. Persistence of the Epstein-Barr virus and the origins of associated lymphomas. *N Engl J Med* 2004; **350**: 1328-1337 [PMID: 15044644 DOI: 10.1056/nejmra032015]

177 **Vockerodt M**, Yap LF, Shannon-Lowe C, Curley H, Wei W, Vrzalikova K, Murray PG. The Epstein-Barr virus and the pathogenesis of lymphoma. *J Pathol* 2015; **235**: 312-322 [PMID: 25294567 DOI: 10.1002/path.4459]

178 **Smith MA**, Irving PM, Marinaki AM, Sanderson JD. Review article: malignancy on thiopurine treatment with special reference to inflammatory bowel disease. *Aliment Pharmacol Ther* 2010; **32**: 119-130 [PMID: 20412066 DOI: 10.1111/j.1365-2036.2010.04330.x]

179 **Dayharsh GA**, Loftus EV Jr, Sandborn WJ, Tremaine WJ, Zinsmeister AR, Witzig TE, Macon WR, Burgart LJ. Epstein-Barr virus-positive lymphoma in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. *Gastroenterology* 2002; **122**: 72-77 [PMID: 11781282 DOI: 10.1053/gast.2002.30328]

180 **Subramaniam K**, D'Rozario J, Pavli P. Lymphoma and other lymphoproliferative disorders in inflammatory bowel disease: a review. *J Gastroenterol Hepatol* 2013; **28**: 24-30 [PMID: 23094824 DOI: 10.1111/jgh.12015]

181 **Kandiel A**, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005; **54**: 1121-1125 [PMID: 16009685 DOI: 10.1136/gut.2004.049460]

182 **Posthuma EF**, Westendorp RG, van der Sluys Veer A, Kluin-Nelemans JC, Kluin PM, Lamers CB. Fatal infectious mononucleosis: a severe complication in the treatment of Crohn's disease with azathioprine. *Gut* 1995; **36**: 311-313 [PMID: 7883236 DOI: 10.1136/gut.36.2.311]

183 **N'guyen Y**, Andreoletti L, Patey M, Lecoq-Lafon C, Cornillet P, Léon A, Jaussaud R, Fieschi C, Strady C. Fatal Epstein-Barr virus primo infection in a 25-year-old man treated with azathioprine for Crohn's disease. *J Clin Microbiol* 2009; **47**: 1252-1254 [PMID: 19193838 DOI: 10.1128/JCM.02052-08]

184 **Honkila M**, Niinimäki R, Taskinen M, Kuismin O, Kettunen K, Saarela J, Turunen S, Renko M, Tapiainen T. 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 [PMID: 31077135 DOI: 10.1186/s12879-019-4022-3]

185 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

186 **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**: 276-283 [PMID: 32359205 DOI: 10.1111/apt.15804]

187 **D'Amico F**, Danese S, Peyrin-Biroulet L. Systematic Review on Inflammatory Bowel Disease Patients With Coronavirus Disease 2019: It Is Time to Take Stock. *Clin Gastroenterol Hepatol* 2020; **18**: 2689-2700 [PMID: 32777550 DOI: 10.1016/j.cgh.2020.08.003]

188 **Allocca M**, Chaparro M, Gonzalez HA, Bosca-Watts MM, Palmela C, D'Amico F, Zacharopoulou E, Kopylov U, Ellul P, Bamias G, Ntelis V, Lahat A, Mantzaris GJ, Papaconstantinou I, Katsanos K, Uspenskaya Y, Christodoulou D, Ben Horin S, Peyrin-Biroulet L, Torres J, Sebastian S, Gisbert JP, Danese S, Fiorino G. Patients with Inflammatory Bowel Disease Are Not at Increased Risk of COVID-19: A Large Multinational Cohort Study. *J Clin Med* 2020; **9** [PMID: 33142843 DOI: 10.3390/jcm9113533]

189 **Bossa F**, Carparelli S, Latiano A, Palmieri O, Tavano F, Panza A, Pastore M, Marseglia A, D'Altilia M, Latiano T, Corritore G, Martino G, Nardella M, Guerra M, Terracciano F, Sacco M, Perri F, Andriulli A. Impact of the COVID-19 outbreak and the serum prevalence of SARS-CoV-2 antibodies in patients with inflammatory bowel disease treated with biologic drugs. *Dig Liver Dis* 2021; **53**: 277-282 [PMID: 33423942 DOI: 10.1016/j.dld.2020.12.120]

190 **Scribano ML**. Why Do Immunosuppressed Patients with Inflammatory Bowel Disease Not Seem to Be at a Higher Risk of COVID-19? *Dig Dis Sci* 2020; Online ahead of print [PMID: 33073335 DOI: 10.1007/s10620-020-06624-5]

191 **Bezzio C**, Saibeni S, Variola A, Allocca M, Massari A, Gerardi V, Casini V, Ricci C, Zingone F, Amato A, Caprioli F, Lenti MV, Viganò C, Ascolani M, Bossa F, Castiglione F, Cortelezzi C, Grossi L, Milla M, Morganti D, Pastorelli L, Ribaldone DG, Sartini A, Soriano A, Manes G, Danese S, Fantini MC, Armuzzi A, Daperno M, Fiorino G; 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**: 1213-1217 [PMID: 32354990 DOI: 10.1136/gutjnl-2020-321411]

192 **Pan L**, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y, Niu X, Ping R, Du Y, Li T, Xu G, Hu Q, Tu L. Clinical Characteristics of COVID-19 Patients With Digestive

Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *Am J Gastroenterol* 2020; **115**: 766-773 [PMID: 32287140 DOI: 10.14309/ajg.0000000000000620]

193 **Zingone F**, Savarino EV. Viral screening before initiation of biologics in patients with inflammatory bowel disease during the COVID-19 outbreak. *Lancet Gastroenterol Hepatol* 2020; **5**: 525 [PMID: 32220656 DOI: 10.1016/S2468-1253(20)30085-6]

194 **Nakase H**, Matsumoto T, Matsuura M, Iijima H, Matsuoka K, Ohmiya N, Ishihara S, Hirai F, Wagatsuma K, Yokoyama Y, Hisamatsu T. Expert Opinions on the Current Therapeutic Management of Inflammatory Bowel Disease during the COVID-19 Pandemic: Japan IBD COVID-19 Taskforce, Intractable Diseases, the Health and Labor Sciences Research. *Digestion* 2020; 1-9 [PMID: 32892197 DOI: 10.1159/000510502]

195 **Magro F**, Rahier JF, Abreu C, MacMahon E, Hart A, van der Woude CJ, Gordon H, Adamina M, Viget N, Vavricka S, Kucharzik T, Leone S, Siegmund B, Danese S, Peyrin-Biroulet L. Inflammatory Bowel Disease Management During the COVID-19 Outbreak: The Ten Do's and Don'ts from the ECCO-COVID Taskforce. *J Crohns Colitis* 2020; **14**: S798-S806 [PMID: 32722754 DOI: 10.1093/ecco-jcc/jjaa160]

196 **Siegel CA**, Melmed GY, McGovern DP, Rai V, Krammer F, Rubin DT, Abreu MT, Dubinsky MC; 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**: 635-640 [PMID: 33472895 DOI: 10.1136/gutjnl-2020-324000]

197 **Alexander JL**, Moran GW, Gaya DR, Raine T, Hart A, Kennedy NA, Lindsay JO, MacDonald J, Segal JP, Sebastian S, Selinger CP, Parkes M, Smith PJ, Dhar A, Subramanian S, Arasaradnam R, Lamb CA, Ahmad T, Lees CW, Dobson L, Wakeman R, Iqbal TH, Arnott I, Powell N; Inflammatory Bowel Disease section of the British Society of Gastroenterology and the 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**: 218-224 [PMID: 33508241 DOI: 10.1016/S2468-1253(21)00024-8]

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