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

Craviotto V *et al*. Viral infections in IBD

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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.

**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 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 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 cerebrospinal 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 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.

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**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.

**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  SaO2% < 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*.