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Management of hepatitis B virus infection in patients with inflammatory bowel disease under immunosuppressive treatment

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Abstract

Hepatitis B remains a significant global clinical problem, despite the implementation of safe and effective vaccination programs. The prevalence of hepatitis B virus (HBV) in patients with inflammatory bowel disease (IBD) largely follows the regional epidemiologic status. Serological screening with hepatitis B surface antigen (HBsAg), and antibodies to hepatitis B surface (anti-HBs) and core (anti-HBc) proteins is a key element in the management of IBD patients and, ideally, should be performed at IBD diagnosis. Stratification of individual cases should be done according to the serologic profile and the IBD-specific treatment, with particular emphasis in patients receiving immunosuppressive regimens. In patients who have not contracted HBV, vaccination is indicated to accomplish protective immunity. Vaccination in immunosuppressed patients, however, is a challenging issue and several strategies for primary and revaccination have been proposed. The risk of HBV reactivation in patients with IBD should be considered in both HBsAg-positive and HBsAg-negative/anti-HBc-positive patients, when immunosuppressive therapies are administered. HBV reactivation is preventable *via* the administration of prophylactic nucleot(s)ide analogues and should be the standard approach in HBsAg-positive patients. HBsAg-negative/anti-HBc-positive patients represent a non-homogeneous group and bear a significantly lower risk of HBV reactivation. Biochemical, serological and molecular monitoring is currently the recommended approach for anti-HBc patients. Acute HBV infection is rarely reported in IBD patients. In the present review, we outline the problems associated with HBV infection in patients with IBD and present updated evidence for their management.

Key Words: Hepatitis B virus; Inflammatory bowel disease; Reactivation; Immunosuppression; Vaccination; Prophylaxis

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Core Tip: The management of hepatitis B virus (HBV) infection poses significant challenges for patients with inflammatory bowel disease (IBD). Lower rates of vaccination for HBV have been reported in this population and immunization programs should be encouraged and intensively implemented. In addition, patients who receive immune-modifying therapies may develop suboptimal responses to vaccination. In the presence of present or past HBV infection, immunosuppressive therapies may increase the risk for reactivation of the virus with adverse clinical outcomes. Close surveillance and/or prophylactic anti-viral treatment may be employed depending on the status of HBV infection and the IBD-specific therapy.

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INTRODUCTION

Hepatitis B is among the most common infections worldwide and represents a major global health problem due to its potential for considerable morbidity and mortality. According to a World Health Organization report, in 2015, 257 million people were living with chronic hepatitis B infection[1]. In fact, it has been estimated that approximately one-third of the world's population has been exposed to hepatitis B virus (HBV). HBV infection is a frequent cause of both acute and chronic hepatitis. The latter may result in a variety of outcomes, which range from asymptomatic infection to end-stage liver disease with cirrhosis, hepatocellular cancer and death. Accordingly, it has been reported that HBV infection accounts for 5%-10% of liver transplantations[2]. On the other hand, nowadays, HBV infection is a preventable disease, due to the development and universal application of highly effective and safe vaccines against HBV.

Crohn's disease (CD) and ulcerative colitis (UC), collectively referred to as the inflammatory bowel diseases (IBDs), are immune-mediated diseases that manifest with chronic relapsing inflammation of the gastrointestinal tract. HBV infection may be of particular significance for patients with IBD, due to several factors. Firstly, although initially described as diseases of the West, since the second half of last century, IBDs have displayed accelerating incidence and prevalence rates in developing areas of the world[3-5]. As those regions include countries where HBV is highly prevalent, such trends translate to a constantly increasing number of patients with IBD that may be exposed to and infected with HBV. Secondly, there are reports indicating that patients with IBD may have increased rates of HBV positivity, while, at the same time, vaccination rates may be considerably low in this population. Finally, and more importantly, the mainstay of IBD treatment has been immunomodulatory drugs. Despite the shift from generalized immunosuppression with steroids or thiopurines to selective, targeted immunomodulation *via* biologics or small molecules, various degrees of immune response compromise are expected in IBD patients under treatment[6,7]. This state of acquired immunodeficiency may render patients with IBD more vulnerable to acquisition and to a more severe course of various infectious diseases, which include HBV infection. This also encompasses the danger for reactivating a previously latent HBV infection.

In this review, we will present the current status regarding the complex relationship between HBV and IBD, including updated epidemiological trends, screening and vaccination guidelines, and the associations between immunomodulatory treatment and the various clinical scenarios of anti-HBV immunity.

NATURAL HISTORY OF HBV INFECTION

HBV is a hepatotropic DNA virus that belongs to the Hepadnaviridae family. It is

transmitted sexually, parenterally (by contact with infected body fluids or blood) and perinatally, from a hepatitis B surface antigen (HBsAg)-positive mother to her child (vertical transmission). Following transmission, the HBV virion enters the hepatocyte using a cellular receptor, the sodium taurocholate co-transporting polypeptide (known as NTCP)[8]. The first step in HBV replication is the formation of covalently closed circular DNA (cccDNA) in the cell nucleus, a mini chromosome, which is a key structure for the longevity of the virus[9]. It is also known that fragments of HBV DNA integrate in the human DNA, but this integration is not vital for viral replication. After contact with the virus, the risk of chronic infection largely depends on the age of the subject, being 90% for infants, 25%-50% for toddlers, and 1%-5% for adults[10].

Chronic HBV infection consists of different phases with distinct serologic profiles, as have recently been described[11]. Phase I is the HBeAg-positive chronic HBV infection, formerly known as the immune tolerance phase, which is characterized by the presence of HBsAg and hepatitis B e antigen (HBeAg), very high HBV DNA levels and persistently normal transaminases, with no or minimal necroinflammation in the liver. The second phase is the HBeAg-positive chronic HBV hepatitis, which is characterized by high HBV DNA levels, increased transaminases and moderate to severe necroinflammatory activity and fibrosis in the liver tissue. This phase leads to seroconversion in the majority of cases, with loss of the HBeAg and appearance of antibodies to hepatitis B surface protein (anti-HBs). Phase III is the HBeAg-negative chronic HBV infection, previously known as the inactive carrier state, which is characterized by the presence of antibodies to hepatitis B e protein (anti-HBe), undetectable or low levels of HBV DNA, normal alanine aminotransferase (ALT) levels and HBsAg levels usually below 100 IU/mL. Phase IV is the HBeAg- chronic hepatitis, which is characterized by a moderate/severe necroinflammatory process in the liver, high HBV DNA levels and fluctuating liver enzymes. Phase V is the HBsAg-negative phase, also known as occult HBV infection, which is characterized by the absence of the HBsAg, positivity for antibodies to hepatitis B core protein (anti-HBc), with or without anti-HBs antibodies, usually normal ALT, and not necessarily measurable HBV DNA in the serum but detectable in the liver tissue.

The natural history of HBV depends on the phase of the infection; in patients with chronic hepatitis B, progression to cirrhosis is observed at an annual rate of 2%-2.5%, whereas HBeAg-negative patients exhibit a faster progression, at a rate of 8%-20% per year[12]. Thus, signs and symptoms of portal hypertension should be regularly sought for in this population, as should the degree of liver fibrosis *via* imaging. Furthermore, HBV is strongly associated with hepatocellular carcinoma and patients should be stratified according to the risk for malignancy *via* simple scores like the PAGE-B, which incorporates parameters like age, gender, and platelets[13]. Screening for hepatocellular carcinoma is based on abdominal ultrasounds at 6-mo intervals, with or without alpha-fetoprotein measurement.

HBV REACTIVATION

Reactivation of HBV is a distinct event in the natural history of the infection, that is signified by the recurrence of viral replication in patients with a quiescent disease status. According to the American Association for the Study of Liver Diseases[14], in HBsAg-positive patients, reactivation is defined as either at least 2 Log (or 100-fold) increase in HBV DNA compared with the baseline level or HBV DNA at least 3 Log (or 1000) IU/mL in a patient with previously undetectable HBV DNA or HBV DNA at least 4 Log (or 10000) IU/mL if the baseline level is not available. In HBsAg-negative, anti-HBc-positive patients, reactivation is considered as reappearance of the S antigen or the detection of HBV DNA. It is worth mentioning that there are patients who remain HBsAg-negative upon reactivation. This is genetically determined and related to the presence of additional N-linked glycosylation sites in the major hydrophilic region of the S antigen[15] and with the emergence of viral strains with mutated HBsAg[16]. HBV reactivation in patients under immunosuppression may have a deleterious effect. HBV reactivation presents with a wide range of manifestations, from asymptomatic, mild hepatitis to acute liver failure and death. In some cases, HBV reactivation precipitates the induction of chronic hepatitis B, potentially leading to liver cirrhosis and even hepatocellular carcinoma. Severe flares resulting in hepatic decompensation with an unfavorable outcome, commonly present with jaundice. A flare of hepatitis is defined as an ALT level above 100 U/L and at least 3 times higher than baseline. Patients with acute liver failure as a result of HBV reactivation present with higher HBV viral loads and lower IgM anti-HBc titers as compared with patients

with new onset HBV-related acute liver failure[17].

The major precipitating factor for HBV reactivation is the induction of an immunodeficient state in the host, more commonly *via* the administration of immunosuppressive therapies. This is due to the fact that HBV is controlled through the immunological system by specific T and B cells[18]. It follows that, in the presence of immunosuppression, the virus may regain its ability to proliferate and replicate[14]. This explains why HBV reactivation is of particular significance for patients with IBD, as the latter are often treated with therapies that modify the function of the immune system. It should be noted, however, that the large majority of the data originates from studies in oncology, hematology and rheumatology and that extrapolation of these data to IBD patients should be done with caution[19]. Nevertheless, immunosuppression does take place in treated patients and may be of relevance. As an example, tumor necrosis factor (TNF), which is the target of pivotal treatments for patients with IBD, is known to enhance virus clearance; hence, inhibition of TNF signaling enhances HBV replication[11]. Moreover, HBV has a glucocorticoid responsive element in its genome that is stimulated by the use of steroids, another frequently used therapy during flares of IBD[20].

Besides immunosuppression, HBV reactivation may also depend on both host and viral factors. Male sex has been associated with HBV reactivation in oncology patients [21]. HBsAg-positive patients carry higher risk for reactivation as compared to HBsAg-negative, anti-HBc-positive patients. Furthermore, higher HBV DNA levels before the start of immunosuppression confer an elevated risk of reactivation[22]. Finally, among HBsAg-negative patients, those who are anti-HBc-positive with detectable HBV DNA and undetectable anti-HBs before immunosuppression are more susceptible to reactivation[23].

After immunosuppression is imposed, HBV reactivation develops through sequential distinct stages[14,24]. At first, immunosuppression leads to an increase in HBV DNA, whilst the patient remains asymptomatic and transaminases are normal. Subsequently, hepatitis ensues with increased transaminases, with or without symptoms. In some cases, liver damage at this stage may lead to liver failure and even death. Once immunosuppression is either discontinued or reduced or/and antiviral treatment is initiated, a progressive decline of the HBV DNA is observed and the hepatitis flare resolves. In a small percentage of patients, despite such therapeutic measures, progressive deterioration of liver function may still be observed. Moreover, acute liver failure in patients under immunosuppression is associated with poor short-term prognosis and reduced 21-d overall survival compared with immunocompetent patients[25].

HBV PREVALENCE IN PATIENTS WITH IBD

HBV prevalence exhibits a geographic variability around the world, with areas of low (< 2%), medium (2%-7%) and high (> 8%) endemicity[11]. Highly endemic areas include Southeast Asia, the Pacific (excluding Japan and Australia), sub-Saharan Africa and some Eastern European countries. Areas with intermediate endemicity include South, Central and Southwest Asia, Israel, Japan, Eastern and Southern Europe, Russia and most of Central and South America. Low-endemic areas include North America, Western and Northern Europe, Australia, and parts of South America. The worldwide prevalence of HBV has changed over the last 30 years, due to immigration, improvement of the socioeconomic level and the implementation of mandatory vaccination.

The prevalence of hepatitis B in IBD patients has been investigated in several studies from Europe, Asia and the Americas (Table 1). Older studies from European countries showed higher incidence of hepatitis B core antibody (HBcAb) positivity among IBD patients[26,27]. Nevertheless, in more recent reports from Italy[28] and France[29], the prevalence of HBV infection among IBD patients was not different from that in the general population. Similarly, results of two Greek studies also reported prevalence of 2.3%-5% among IBD patients, which was in accordance to what was expected[30,31]. In addition, a study from Poland, a country with intermediate endemicity, also showed that the prevalence of HBV infection among IBD patients was comparable to that of the general population[32]. The most recent study by Losurdo *et al*[33], published in 2020, evaluated the burden of viral hepatitis in IBD and demonstrated that HCV was more frequent than HBV infection in IBD patients but with low overall prevalence.

Table 1 Studies investigating hepatitis B virus prevalence in inflammatory bowel disease patients

Ref.	Type of study; Country	Patients	HBsAg-positive	Anti-HBc-positive	Anti-HBs-positive	Comments
Losurdo <i>et al</i> [33], 2020	Single-center cohort; Italy	807 IBD 438 CD 369 UC	0.9%	7.7%		Similar to regional prevalence
Fousekis <i>et al</i> [31], 2019	Retrospective single-center; Greece	602 IBD	5.3%	13.4%	32.4%	Similar to regional prevalence
Silva <i>et al</i> [94], 2019	Cross-sectional; Brazil	306 IBD 165 UC 141CD	0.7%			Similar to regional prevalence
Chou <i>et al</i> [95], 2019	Retrospective; Taiwan	190 IBD 80 CD 110 UC	13.3%			Higher prevalence of HBsAg in IBD
Yeo <i>et al</i> [96], 2018	Prospective cohort; Korea	210 IBD 109 UC 101 CD	3.8%	26.2%		Treatment-naïve similar prevalence
Chen <i>et al</i> [35], 2017	Retrospective; China	980 IBD 334 UC 646 CD	7.9% 8.1% 7.7%	41.2% 52.7% 35.3%	46.6% 48.8% 45.5%	Higher prevalence of HBsAg in IBD
Harsh <i>et al</i> [34], 2017	Retrospective; India	908 IBD 581 UC 327CD	2.4% 2.2% 2.8%			Similar to regional prevalence
Waszczuk <i>et al</i> [32], 2016	Prospective cross-sectional; Poland	147 IBD		14.3%		Similar to regional prevalence
Chan <i>et al</i> [97], 2016	Retrospective cohort; China	406 IBD	5.7%			Similar to regional prevalence
He <i>et al</i> [98], 2015	Retrospective; China	449 CD 226 UC	13.6% 16.8%	25.4% 30.1%	31.2% 24.3%	Similar to regional prevalence
Ben Musa <i>et al</i> [47], 2014	Retrospective observational; United States	500 IBD	1.8%	3.2%		Similar to regional prevalence (screening rate 51%)
Huang <i>et al</i> [99], 2014	Retrospective; China	714 IBD	5.5%	40.6%	21.6%	Higher prevalence of HBsAg in IBD patients
Kim <i>et al</i> [37], 2014	Observational; Korea	513 IBD 241 CD 272 UC	3.7% 4.1% 3.3%			Similar to regional prevalence
Papa <i>et al</i> [28], 2013	Prospective; Italy	301 IBD	0.3%	7.3%		Similar to regional prevalence
Park <i>et al</i> [93], 2012	Retrospective; Korea	4153 IBD 1521 CD 1728 UC	4.1% 3.6% 4.6%			Similar to regional prevalence
Katsanos <i>et al</i> [30], 2010	Retrospective; Greece	482 IBD	2.3%			Similar to regional prevalence
Chevaux <i>et al</i> [100], 2010	Hospital-based; France	315 IBD 252 CD 63 UC			48.9% 2.8% 1.6%	Similar to regional prevalence
Loras <i>et al</i> [101],	Multicenter Hospital-based;	2076 IBD				Similar to regional prevalence

2009	Spain	1128 CD	0.6%	7.1%	17%	
		928 UC	0.8%	8%	14.9%	
		20 IC	0	5.3%	17.6%	
Tolentino <i>et al</i> [27], 2008	Hospital-based; Brazil	102 CD	0	43.3%		Higher prevalence of anti-HBc patients
		74 UC	2.3%	56.7%		
Esteve <i>et al</i> [102], 2004	Multicenter; Spain	80 CD	7.5%			Screening prior to anti-TNF treatment
Biancone <i>et al</i> [26], 2001	Multicenter; Italy	332 CD	2.1%	10.9%	14.4%	Higher prevalence of HBsAg in IBD
		162 UC	0.6%	11.5%	15.8%	

CD: Crohn's disease; HBc: Hepatitis B core protein; HBs: Hepatitis B surface protein; HBsAg: Hepatitis B surface antigen; IBD: Inflammatory bowel disease; TNF: Tumor necrosis factor; UC: Ulcerative colitis.

Studies from parts of the world with high HBV endemicity have also been published. In a report from India, the prevalence of HBV among 908 CD and UC patients was 2.8% and 2.2% respectively, both being comparable to the national prevalence of HBV[28]. Interestingly, HBV prevalence was higher in patients with intestinal tuberculosis than in IBD patients[34]. Data from China are contradictory; the prevalence of ongoing HBV infection in IBD patients paralleled that in the general population (7.86% and 7.3%)[29]. However, when assessing the prevalence of both present and past infection (HBsAg-positive and HBsAg-negative, anti-HBc positive) prevalence was significantly greater in IBD patients than in healthy individuals[35]. Additionally, in this group of patients, age above 30 years, UC and previous surgery were found to be the main risk factors[35]. Two studies from Korea, a highly endemic area for HBV with predominantly vertical/perinatal mode of transmission, demonstrated higher prevalence of HBV infection among IBD patients than in the western countries, but similar to the Korean general population[36,37]. It is noteworthy that, in the above studies, HBV DNA was not determined in anti-HBc-positive patients, and therefore the true frequency of occult hepatitis B was not determined.

Taken together, the majority of available evidence support the hypothesis that the cumulative prevalence of HBV in IBD patients parallels the national trends for HBV infection in each country. This is particularly true for European countries and, overall, indicates that IBD alone does not seem to constitute a risk factor for hepatitis B.

MANAGEMENT OF HBV INFECTION IN PATIENTS WITH IBD

All patients who have been diagnosed with IBD should be screened for their immunological status regarding exposure to HBV, preferably at the time of diagnosis. Unfortunately, surveys conducted by the European Liver Patients Association (commonly known as the ELPA) suggest that up to 90% of HBV-infected people in Europe are unaware of their condition[38]. It is, therefore, of great importance that patients be screened upon diagnosis and that the screening be performed in a pre-defined manner *via* the implementation of checklists provided by International societies[7,39,40]. It is obvious that such practice is of far greater significance for those patients who are scheduled to commence immunosuppressive therapy[7].

Initial screening should include testing for HBsAg, as well as anti-HBc and anti-HBs[7]. Based on the results from these tests, the immunization status may fall into one of three categories that should be then managed appropriately (Table 2).

HBsAg-negative, anti-HBs-negative, anti-HBc-negative patients

Patients who test negative for all three serological markers are susceptible to HBV infection upon contact with the virus. Currently, vaccination is recommended to all HBsAg-negative patients who are also negative for both anti-HBc and anti-HBs[7].

Encouraging immunization is very important. Treating gastroenterologists should explain the advantages of vaccination, while reassuring patients and providing them with vaccine-related information, as this will lead to better compliance and increased participation in vaccination programs[41,42]. Constant training of the physicians and participation in educational activities is similarly important, because gaps in the knowledge of gastroenterologists regarding vaccinations have been reported[43].

Table 2 Serologic profiles after initial screening

	HBsAg	Anti-HBc	Anti-HBs
Susceptible	Negative	Negative	Negative
Immune due to vaccination	Negative	Negative	Positive
HBV infection	Positive	Positive	Negative
Resolved HBV infection or occult HBV infection	Negative	Positive	Positive or negative

HBc: Hepatitis B core protein; HBs: Hepatitis B surface protein; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

Implementation of a thorough guidance regarding vaccines has been shown to improve the overall adherence to vaccination guidelines[44].

Overall, vaccination rates in IBD patients have been reported to be low[45]. Memled *et al*[46] reported an overall vaccination rate of 28%, which reflects the fact that immunization history is often omitted. Even in tertiary centers, only half of IBD patients may have been screened for HBV[47]. Nevertheless, vaccination attitudes may be changing, nowadays, as improvements in HBV immunization practices for IBD patients have been documented during the last decades. According to Shah *et al*[48], only 8.1% of patients were vaccinated in 2003, *vs* 43.2% in 2011[48]. In this study, between 2003-2011, an overall HBV screening rate of 23.7% in a population of IBD patients under anti-TNF treatment was recorded. Another study from the Netherlands, spanning from 2000 to 2010, showed that the screening rates increased from 36% to 49% during the last 2 years of the study[49]. According to a more recent study of 1834 anti-TNF-naïve patients, HBV screening rates significantly improved between 2010 and 2019 (64% and 87.4% respectively)[50].

Available vaccines for HBV constitute the first- (plasma-derived), second- (yeast- or mammalian-derived recombinant major S antigen) and third-generation (major S and pre-S1 and -S2 proteins) vaccines (Table 3). Vaccines are further differentiated into single antigen vaccines, such as Engerix-B® (GlaxoSmithKline Biologicals, Rixensart, Belgium), HBVaxPRO® (Sanofi-Pasteur, Lyon, France), Recombivax® (Merck & Co, Inc, Kenilworth, NJ, United States), Hepelisav-B® (HepB-CpG; Dynavax Technologies, Emeryville, CA, United States), Fendrix® (GlaxoSmithKline Biologicals), Sci-B-Vac® (VBI Vaccines, Cambridge, MA, United States) and combination vaccines like Twinrix® (GlaxoSmithKline Biologicals) (HBV + hepatitis A virus) and Pediarix® (GlaxoSmithKline Biologicals) (HBV + diphtheria/tetanus/whooping cough (pertussis) + polio).

The standard vaccination schedule in IBD patients is the same as that with the general population, which consists of three standard doses of rHBsAg (20 µg) at months 0, 1 and 6, although deviations do occur in practice. For example, Indian guidelines recommend a double-dose, accelerated three-dosing scheme of 40 IU/mL in 0-1-2 mo[51]. Furthermore, in 2018, a novel recombinant vaccine was approved (Hepelisav-B® - HepB-CpG), which bears a unique adjuvant sequence and is administered in two doses, 1 mo apart. This two-dose vaccine has shown promising results in individuals with risk factors for hyporesponsiveness (see below) but has not yet been tested in IBD patients specifically[52].

After completion of the dosing schedule, titers of anti-HBs should be checked within 1-3 mo to confirm the establishment of adequate anti-HBV immunological status, which is signified by detection of anti-HBs antibodies in the serum. In healthy individuals, HBV vaccination confers > 90% protective immunity. In contrast, it has been demonstrated that response rates after HBV vaccination are reduced compared with healthy individuals[53]. Indeed, it was shown that patients with future diagnosis of IBD had suboptimal vaccination response even before the clinical manifestation of IBD[54]. Based on a meta-analysis by Jiang *et al*[53], which included 13 studies with 1688 patients, the pooled response rate to vaccination for HBV among IBD patients was 61%. Rates were not affected by the specific diagnosis of CD or UC[55]. Not only are the rates of anti-HBs positivity decreased in patients with IBD but the titers of antibodies are also lower. In various studies, the reported average anti-HBs titers in healthy individuals after successful immunization were 720[56] and 822[57] IU/mL. In comparison, IBD patients under anti-TNF therapy had reported average values around 245 IU/mL[56]. This was also confirmed by another study by Belle *et al*[58], wherein median anti-HBs levels after vaccination were significantly lower in immunosuppressed patients (253 IU/mL *vs* 497 IU/mL). The significance of such differences is further exemplified by the fact that post-vaccination targets for anti-HBs titers may

Table 3 Available vaccines

	Company	Antigen - Adjuvant	Posology	Dosing
Engerix-B®	GlaxoSmithKline	Rec. major S Ag (yeast) Aluminum	1 mL	3- or 4-dose
			20 mcg	0-1-6 mo
				0-7 d-21 d-12 mo
HBVaxPRO®	Sanofi-Pasteur MSD	Rec. major S Ag (yeast) Aluminum	1 mL	3- or 4-dose
			5 mcg	0-1-6 mo
			10 mcg	0-1-2-12 mo
			40 mcg	
Fendrix®	GlaxoSmithKline	Rec. major S Ag (yeast) Aluminum + 3-O-desacyl-1-4 - monophosphoryl lipid A	0.5 mL	4-dose
			20 mcg	0-1-2-6 mo
Hepelisav-B®	Dynavax	Rec. major S Ag (yeast) HepB-CpG ligand	0.5 mL	2-dose
			20 mcg	0-1 mo
Twinrix®	GlaxoSmithKline	In.HAV + Rec. major S Ag (yeast) Aluminum	1 mL	3-dose
			720/20 mcg	0-7-21 d
				0-1-6 mo
Sci-B-Vac®	VBI Vaccines	Major S Ag, minor pre-S1 + pre-S2 Ag (mammalian cell) Aluminum	1 mL	3-dose
			10 mcg	0-1-6 mo
Pediatrix®	GlaxoSmithKline	DTaP + inactivated poliovirus + Rec.S (yeast) Aluminum	0.5 MI	3-dose
			10 mcg	(6-8 wk interval)

Ag: Antigen; DTaP: Diphtheria-tetanus-whooping cough (pertussis); In.HAV: Inactivated hepatitis A virus; Rec.: Recombinant.

differ between IBD patients and healthy controls. In immunocompetent individuals, a titer above 10 IU/mL is considered adequate; whereas, in immunosuppressed patients, a higher titer, of 100 IU/mL, is considered protective[51]. Indeed, according to Loras *et al*[59], a distinction is made based on the quantity of the antibodies in the serum between seroprotection for titers > 10 IU/mL and effective vaccination for titers > 100 IU/mL.

Factors that have been associated with an inadequate immune response to HBV vaccine have included older age, immunosuppressive therapy, and incomplete dosing (< 3 doses administered)[53,60]. In addition, Altunoz *et al*[55] noted a negative correlation between disease activity and adequate antibody response both for CD and UC. In another study, it was found that ileal disease correlated with lower responses to Engerix-B®. From an interesting perspective, gut microbiota was recently implicated as a regulator of immune response to vaccination. Experimental data from germ-free mice showed reduced response rates after vaccination, which were ameliorated after establishing normal microbiome[61]. As patients with IBD demonstrate intestinal dysbiosis, it could be hypothesized that the latter may negatively affect immunization in a similar manner. Nonetheless, such a concept has yet to be proven.

The major factor, however, that has been studied in relation to the efficacy of HBV vaccination in IBD patients has been the administration of immunomodulatory therapies[53]; hence, this has been the subject of research and discussion, given the fact that it affects the majority of people with CD or UC. Therefore, it is generally recommended to proceed with HBV vaccination ideally at the time of IBD diagnosis and preferably before initiating treatment. Among all immunosuppressive therapies anti-TNF treatment is a major negative influencer of HBV vaccination, as stated in the meta-analysis of Jiang *et al*[53]. The effect of anti-TNF treatment on vaccine efficacy in patients with IBD was assessed by Gisbert *et al*[62], who reported a response rate of 46%. On the other hand, in a European study, the response rates after primary vaccination with Engerix-B® in IBD patients, despite being lower in comparison with healthy individuals, were not adversely associated with the use of biologics and immunomodulators[58]. In the study of Loras *et al*[59], total response rates of 59% after first and second vaccination attempts were observed in patients treated with anti-TNF

monotherapy; whereas, in patients under combination therapy, only a 38% seroprotection rate was observed, highlighting the negative effect of combinatorial immunosuppression. Among the various anti-TNF biologics, the use of infliximab correlated with lower antibody response rate (16.7%) compared with adalimumab (48.4%)[56]. In the same study, ustekinumab exhibited 72% antibody response after vaccination. Treatment with vedolizumab does not seem to influence immune response after vaccination based on anti-HBs titers that were determined in the context of a randomized double-blind placebo control trial[63]. These findings are confirmed by recent data from Harrington *et al*[64], whereby 62.5% of IBD patients treated with vedolizumab achieved an anti-HBs level above 10 mIU/mL after a three-dose standard vaccination scheme with Engerix-B®, which is comparable to the response of immunocompetent patients. Data regarding the effect of treatment with tofacitinib on the vaccination efficacy in IBD patients are scarce. Studies in rheumatology show that it is associated with diminished response to pneumococcal but not influenza vaccination[65]. In a small retrospective study of patients with rheumatoid arthritis on tofacitinib, only 2 HBsAg-positive patients, who did not receive prophylaxis, developed reactivation[66].

Based on the aforementioned results, it appears that patients with IBD who are treated with immune-modifying agents may exert suboptimal immunization status after HBV vaccination. Consequently, strategies to improve efficacy have been implemented with various results (see next paragraph). Such approaches include accelerated, repeated or increased dosing, whereas different vaccines may also display diverse efficacies. Nevertheless, the most valuable approach may be the selection of the appropriate timepoint for vaccination. In fact, early vaccination of young patients who have not received any immunosuppressants is the best strategy for optimal immune response.

Gisbert *et al*[67] tested a protocol combining both increased dose and shorter intervals of vaccination using double-dose of Engerix-B® given in 0-1-2 mo. This accelerated scheme achieved an improvement in immunization rates from 41% to 75% compared with the standard protocol. Loras *et al*[59] used the same scheme for the vaccination of IBD patients under anti-TNF treatment and found a 57% response rate. A study by Chaparro *et al*[68] compared the double-dose Engerix-B® vaccine given in a four-dose schedule (0-1-2-6 mo intervals) with the single-dose Fendrix® given in the same intervals. The two vaccines demonstrated equivalent effectiveness rates but the four-dose protocol exhibited enhanced efficacy (range: 68%-75%) in achieving anti-HBs titers above 100 IU/mL. In another recent study by Haykir *et al*[56], comprising a standard schedule high-dose immunization program for a mixed population of IBD and rheumatology patients under immunosuppression, did not significantly improve the immune response. Similarly, use of third-generation vaccines (*e.g.*, Sci-B-Vac®) did not show any additional benefit compared with second-generation vaccines (*e.g.*, Engerix-B®)[69], despite elucidating higher response rates in immunocompetent healthy individuals. Taken together, these studies show that intensified protocols may accomplish higher rates of effective immunization. The variety of such approaches indicates that each IBD center should test and propose its own protocols, based on local experience, efficacy rates and available options.

Patients who have been effectively immunized should be monitored at least every 2 years, by assessing anti-HBs titers. It has been shown that 18% of patients lose their antibodies on a yearly basis[69,70]. In the case that the first immunization attempt is unsuccessful, several revaccination strategies have been proposed (Table 4). The most common approach in this setting entails the repetition of a standard three-dose scheme. Indeed, a three-dose revaccination schedule yielded better response rates (62.9%) than a single-dose or 2 additional doses (40.2%), when evaluated according to patient ability to mount an anti-HBs titer above 10 IU/mL, emphasizing the need of completion of the three-dose schedule[71]. The same three-dose revaccination approach in the study of Cossio-Gil *et al*[60] achieved a response rate of 52.8%. However, in these studies, an anti-HBs threshold of 10 IU/mL, instead of 100 IU/mL, was used. Levels of anti-HBs between 10-100 IU/mL after first vaccination are correlated with effective protective immunity characterized by obtaining anti-HBs > 100 IU/L after revaccination[59]. The response rate for patients older than 35 years who initially developed anti-HBs titer < 10 IU/mL was only 25% after repeat vaccination[59].

The Turkish society of gastroenterology recommends a response-guided approach based on anti-HBs titers after primary vaccination[72]. In patients with undetectable and/or < 10 IU/mL anti-HBs levels a double-dose, 0-1-6 mo complete revaccination scheme is proposed; whereas, in patients with anti-HBs levels between 10-100 IU/mL, a single double-dose booster dose is administered[72]. In healthy individuals without

Table 4 Revaccination studies for hepatitis B virus in inflammatory bowel disease

Ref.	Study	Patients, n	Strategies	Response rate for anti-HBs
Pratt <i>et al</i> [71], 2019	Retrospective cohort	149	3-dose schedule vs 1 or 2 doses	62.9% 40.2% (> 10)
Cossio-Gil <i>et al</i> [60], 2015	Retrospective cohort	53	3-dose schedule	52.8%
Loras <i>et al</i> [59], 2014	Prospective	389	Double-dose 0-1-2	31.3% (> 100) 44.4% (10-100)

HBs: Hepatitis B surface protein.

adequate immune response after primary vaccination with Engerix-B®, the use of a different vaccine (*i.e.*, Fendrix® or HBVaxPRO®) for revaccination resulted in improved response rates[73]. However, this practice has not been evaluated in IBD patients. At present, the optimal revaccination protocol in this population is unknown and further studies are needed. Vaccination for hepatitis B is generally considered safe. Injection site reactions and mild systemic adverse events are the most commonly reported problems[1]. HBV vaccination does not influence the course of IBD.

HBsAg-positive patients

Patients who test positive for HBsAg have ongoing HBV infection and are at the highest risk for reactivation if their disease is quiescent at baseline. Those patients should be initially tested with complete blood count and for levels of ALT, aspartate aminotransferase, albumin, and HBV DNA, as well as undergoing liver stiffness measurement and tests for other hepatitis virus (*e.g.*, hepatitis D virus). Results from those tests will help assess HBV status and evaluate the need for antiviral treatment and monitoring[7,11]. Patients who have HBsAg-positive and HBeAg-positive or -negative chronic hepatitis B [HBV DNA > 2000 IU/mL, ALT > upper limit of normal and/or at least moderate liver necroinflammation or fibrosis] need to receive antiviral treatment, irrespective of type of immunosuppression[11]. HBsAg-positive patients with IBD who will commence treatment with immune-modifying medications are at risk for reactivation of HBV. Factors that relate to HBV reactivation in IBD patients include infection status, level of immunosuppression and duration of immunosuppressive therapy.

Various guidelines have been offered as to the optimal course of action regarding the management of HBsAg-positive patients with IBD[7,11]. As a general rule, all HBsAg-positive patients with either chronic infection or hepatitis should receive prophylactic antiviral treatment before starting any type of immunosuppressive treatment[7,11,51]. The only exception is the statement from the American Gastroenterological Association (AGA)[74], whereby guidelines are diversified according to the estimated risk for HBV reactivation into high (> 10%), moderate (1%-10%) and low (< 1%) risk. In IBD patients, the therapy conferring high risk of reactivation is prednisone ≥ 10 mg daily for ≥ 4 wk. Therapies with moderate risk include TNF-α inhibitors, cytokines or integrin inhibitors and prednisone < 10 mg daily for ≥ 4 wk. Low risk for reactivation is conferred by treatment with traditional immunosuppressive agents (azathioprine, methotrexate) and any dose of oral steroids for ≤ 1 wk or low dose (< 10 mg daily) for ≥ 4 wk. Accordingly, high and moderate risk individuals should receive prophylactic nucleos(t)ide therapy, whereas patients at moderate risk are given the option for monitoring. The AGA recommends that antiviral treatment should be continued for at least 6 mo after discontinuation of the immunosuppressants[74]. In patients at low risk for reactivation, monitoring is sufficient. In addition, combination of immunomodulatory medications increases the risk of reactivation. In a multicenter Spanish study, Loras *et al*[59] demonstrated a pronounced risk of HBV reactivation in HBsAg-positive patients receiving ≥ 2 immunosuppressants without antiviral prophylaxis.

It should be noted that these recommendations are primarily based on data derived from oncology, rheumatology and hematology studies[75-77]. The extension of these conclusions in IBD patients is precarious, since differences do exist. In particular, the duration of treatment differs considerably between the two groups. Chemotherapy is usually offered for a finite number of treatment cycles. In contrast, IBD treatments may last life-long. In relevance to this, it should be remembered that HBV is not a direct

cytopathogenic virus and that liver cell damage in chronic hepatitis B is the result of immune system activation against the infected cells. As a result, a hepatitis flare is not observed during the time of maximal immunosuppression but at a later time point. Thus, anti-viral therapy should be continued for at least 12 mo after the cessation of any immunosuppressive therapy in patients with immune-mediated diseases, including IBD[78].

Nucleos(t)ide analogs are the preferred antiviral therapy in patients with IBD who will receive immunosuppression, as long-term treatment is an effective and safe strategy. In contrast, the use of pegylated-interferon is discouraged. The third-generation antivirals of tenofovir, entecavir and tenofovir alafenamide are recommended, due to their high antiviral activity with practically no resistance (antivirals with high resistance barrier). Entecavir or tenofovir alafenamide should be preferred over tenofovir in patients above 60 years of age, in patients with a history of bone disease (*i.e.*, fracture, osteoporosis, chronic steroid use), and in patients with renal dysfunction (with estimated glomerular filtration rate < 60 mL/min/1.1, albuminuria > 30 mg/24 h, or low phosphate < 2.5 mg/dL)[11]. Lamivudine is a good antiviral for short-term use, as the rate of 1-year and 2-year resistance is 20% and 30%, respectively. Given that immunosuppressives for IBD patients are long-term therapies, the use of lamivudine is discouraged. In fact, in a small published study, it was shown that 6 out of 8 IBD patients who received lamivudine prophylaxis required a change to newer antivirals[30].

Antiviral treatment should ideally start 2 wk prior to the commencement of immunosuppression and should be continued for at least 12 mo after treatment cessation, provided that the underlying HBV infection is quiescent.

According to a series of patients with chronic HBV infection and IBD with a long-term follow up (20 years), the natural history of HBV is not affected in this group of patients[36]. Nevertheless, an association between chronic viral hepatitis and non-alcoholic fatty liver disease has been shown in patients with IBD. In a recent study by Losurdo *et al*[33], IBD patients with concurrent chronic viral hepatitis present more frequently with diabetes, wide waist circumference and increased liver stiffness. In addition, the frequent use of steroids, is further considered a risk factor for NAFLD and the combination of liver steatosis and viral hepatitis may sensitize the liver and render it more vulnerable to developing liver-associated complications. These facts further emphasize the need for prophylaxis and treatment strategies for HBV in patients with IBD.

HBsAg-negative/anti-HBc-positive patients

Patients with isolated anti-HBc antibodies on serological testing represent a non-homogenous population. This serologic profile reflects either a false positive result particularly in regions of low endemicity or corresponds to the 'window' period before the appearance of anti-HBs, as in the case of resolved HBV infection. Moreover, isolated anti-HBc antibodies in the presence of undetectable anti-HBs may be found in a patient with resolved HBV infection, due to waning immunity after many years or to treatment with immunomodulating therapy. The latter scenario is of potential significance for the IBD patient, as it carries risk for HBV reactivation. This risk is lower than in HBsAg-positive patients, and is estimated to be between 4%-5%, based primarily on findings from oncological studies. In a meta-analysis by Cholongitas *et al* [79], the risk of HBV reactivation in anti-HBc-positive patients with non-hematological diseases was 3.6%. Quantification of anti-HBc antibodies can help distinguish occult hepatitis B infection from a past HBV infection, with a cutoff of 6.6 IU/mL[80]. Detection of anti-HBc antibodies serves as a surrogate marker of occult HBV infection, which is defined as the detection of HBV DNA in the liver tissue (gold standard) or in the blood[23].

The prevalence of occult HBV infection in this particular subgroup of patients varies, depending on the HBV DNA threshold used (200 U/mL) and ranges between 11%-89%[81]. More recent data indicate detectable HBV DNA in 0-27% of patients with exclusive anti-HBc positivity[82]. When IBD populations were exclusively examined, the rates of anti-HBc positivity were highly dependent on the HBV endemicity. Data from low endemicity areas such as Italy and France range from 7.7% [33] to 0.6%[29] respectively, whereas data from eastern Europe (intermediate endemicity region) indicate a prevalence of 12%. In an HBV endemic area, anti-HBc positivity was 41.2%[35]. The risk of HBV reactivation depends also on the specific state of immunodeficiency, including the particular immunosuppressive therapy, being significantly higher in patients with malignant hematological diseases and especially with the use of the anti-CD20 agent rituximab.

The first case of HBV reactivation in an IBD patient with isolated anti-HBc positivity was reported in 2006, involving a woman with CD who was treated with infliximab [83]. Ever since, studies assessing the reactivation probability in patients under anti-TNF treatment have been performed, ultimately confirming a low risk of reactivation. Indeed, the reported reactivation rates vary between 3.13% [84] and 7% [59]. It has been reported that the risk of reactivation may be higher with the use of infliximab than with the other anti-TNFs [85].

When an anti-HBc-positive patient is scheduled to start therapy with immunomodifying medications, he should have an evaluation for HBV DNA presence in the blood. In the case of detectable HBV DNA, the patient is treated as being HBsAg-positive. The management of patients showing negativity for HBV DNA is not equally straightforward, particularly in patients with IBD, as literature is scarce. According to the AGA guidelines, anti-HBc-positive, HBV DNA-negative IBD patients who receive corticosteroids in high dose (> 20 mg prednisone daily) or moderate dose (10-20 mg prednisone daily for ≥ 4 wk) and/or anti-TNFs should receive antiviral prophylaxis over monitoring [74]. Antivirals should be continued for at least 6 mo after stopping immunosuppressants. It should be noted, however, that the level of evidence is “weak recommendation/moderate quality evidence” and, thus, the alternative for monitoring is also an acceptable option. According to the European Association for the Study of the Liver (commonly referred to as the EASL) and the European Crohn’s and Colitis Organisation (commonly referred to as the ECCO) guidelines, surveillance is strongly indicated and includes monitoring of transaminases, HBsAg, anti-HBs antibodies and HBV DNA, in the first month of treatment and every 3 mo thereafter. Pre-emptive antiviral therapy is commenced in the case of HBsAg seroconversion or HBV DNA detection. If monitoring cannot be ensured, it would be prudent to adopt the approach of the AGA and start prophylactic antiviral therapy. Accessibility to regular testing and follow-up as well as patient preferences should also be incorporated in decision-making. Treatment with azathioprine, 6-mercaptopurine or methotrexate in anti-HBc-positive patients carries a low risk of reactivation.

The frequency of anti-HBs in anti-HBc patients is approximately 75%. Emerging evidence suggests that HBV reactivation is most likely in those with low or undetectable anti-HBs levels [86]. The protective role of anti-HBs was illustrated in a meta-analysis by Paul *et al* [86], where patients with detectable anti-HBs had 79% lower odds of reactivation. Nevertheless, in the same meta-analysis, it is noted that HBV reactivation still occurs in patients with both anti-HBc positivity and anti-HBs positivity. In lymphoma patients, undetectable anti-HBs or titers of 10-100 mIU/mL at baseline are independent predictive factors for reactivation compared with anti-HBs titers of ≥ 100 mIU/mL [87]. Furthermore, in lymphoma patients treated with chemotherapy, quantification of anti-HBc and anti-HBs might help to predict HBV reactivation. High anti-HBc (6.41 IU/mL) and low anti-HBs (< 56.48 mIU/mL) at baseline are associated with a higher risk of reactivation (hazard ratio: 517.29; $P < 0.001$) [88]. However, this approach has not been evaluated in IBD patients. The proposed strategy according to ECCO guidelines for patients with anti-HBc and/or anti-HBs positivity is monitoring [7].

Acute HBV infection

Acute HBV infection during the course of IBD is a rare occurrence. Limited data exist in the literature and only few clinical cases have been described. Data from these case reports are inconsistent, underlining the variable evolution of acute HBV infection in immunocompromised IBD patients. In the case of a patient who developed acute hepatitis B, infliximab was temporarily discontinued, until antiviral treatment was commenced without further complications [48]. In contrast, a young CD patient on infliximab developed acute HBV infection that rapidly evolved to fatal liver failure [89].

In healthy adult individuals, acute HBV infection leads to resolution in approximately 90% of cases; whereas, in immunosuppressed patients, spontaneous recovery rates are reduced [90]. The diagnosis of acute hepatitis B infection is based on the detection of IgM anti-HBc. Yet, anti-HBc IgM are also detected during exacerbations of chronic hepatitis B. Quantitative measurement of anti-HBc IgM may be helpful in differentiating acute HBV infection from a flare of a chronic infection, as lower levels are detected in the latter [91]. Specific threshold values depend on the assay used. For instance, when applying chemiluminescent immunoassay (also commonly known as CLIA), levels > 10 show 100% sensitivity and 99% specificity [92] and levels > 8 show sensitivity of 96.2% and specificity of 89.7% [93]. Similarly, for HBV DNA, lower levels are observed in acute *vs* a flare of chronic HBV infection [91].

Kinetics of HBsAg have been used to predict the likelihood of chronicity, as a 50% reduction within 4 wk is predictive of resolution of HBV infection[91]. Prevention of liver failure is the therapeutic goal in acute hepatitis B in immunocompetent adults. This is why only patients with a protracted course or coagulopathy are candidates for antiviral treatment. In immunosuppressed patients, however, timely initiation of nucleos(t)ide analogues is suggested in order to avert the progression to liver failure.

CONCLUSION

Despite the implementation of mandatory vaccination of newborns against HBV, hepatitis B remains a significant global clinical problem. As the prevalence of IBD is also growing around the world, a substantial number of CD and UC patients with concomitant HBV infection remains and new cases are expected to occur. Screening of IBD patients with HBV serology is of paramount significance and should be actively communicated among patients and ideally implemented at diagnosis on IBD. The initial vaccination approach for IBD patients is largely similar to the recommendations for the general population, despite a lower reported vaccination efficacy, with considerable variation in revaccination strategies. It should be kept in mind that immunosuppressive treatment increases the risk of HBV reactivation; thus, close monitoring of patients at-risk is required. In the case of HBsAg positivity, antiviral prophylaxis is offered to IBD patients regardless of type of immunosuppression. On the other hand, HBsAg-negative, anti-HBc-positive patients represent a low reactivation risk group, for whom monitoring according to international and local guidelines is indicated.

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