Viral Hepatitis and Inflammatory Bowel Disease

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Viral hepatitis is common worldwide and in the United States. Inflammatory bowel disease (IBD) patients with chronic hepatitis B virus (HBV) with active disease (elevated alanine aminotransferase level and viral replication) should receive HBV treatment. HBV reactivation is associated with significant morbidity and mortality in patients receiving immunosuppression. IBD patients may require long-term immunosuppression, and therefore should be considered candidates for vaccination against new HBV infection as well as prophylaxis against HBV reactivation prior to immunosuppressive therapy. Tumor necrosis factor alpha antagonists and immunomodulators appear compatible with use in IBD patients with HCV, although prednisone may increase viral replication. HCV treatment with peg-interferon and ribavirin may exacerbate gastrointestinal symptoms, and therefore the decision to treat HCV needs to be individualized. Management of IBD patients with viral hepatitis is addressed in this review.

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Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, hepatitis A, hepatitis B, hepatitis C, viral hepatitis, vaccination

Viral hepatitis is a common infection worldwide. An estimated 1.4 million people in the United States and over 350 million people worldwide have chronic hepatitis B virus (HBV) infection.[1,2] An estimated 2.7 million people in the United States and over 250 million people worldwide have chronic HCV.[3] The prevalence of chronic HBV and HCV varies greatly depending on various factors. HBV is associated with perinatal and childhood transmission risk stratified by geography, whereas HCV is associated with social risk factors and exposure to blood products. Chronic viral hepatitis may result in cirrhosis in 5%–25% of infected patients.[1,2] Complications of cirrhosis include coagulopathy, varices, hepatocellular carcinoma, and death.

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory conditions of the gastrointestinal tract collectively referred to as inflammatory bowel disease (IBD). The prevalence of HBV and HCV has been reported to be increased in patients with IBD; therefore, HBV and HCV are important infections to be aware of in patients with IBD. IBD patients may have an increased risk of HBV and HCV due to prior surgery or blood transfusions. Treatment of HBV and HCV may affect the clinical course of IBD and vice versa. Management of IBD patients with viral hepatitis is addressed in this review.

HEPATITIS B

General Concepts

HBV infection can be broadly divided into three categories: active chronic HBV, inactive HBV carrier, and resolved HBV[4] (Table 1). In immunocompetent patients with active chronic HBV, defined by HBV DNA levels $\geq$2000 IU/mL and elevated alanine aminotransferase (ALT) levels, antiviral treatment is indicated. In immunocompetent patients with inactive hepatitis B, defined by HBV DNA levels $\leq$2000 IU/mL and normal ALT levels, antiviral therapy is not indicated but these patients are candidates for prophylactic therapy in the setting of immunosuppressive therapy. Finally, patients with resolved HBV infection, defined by a lack of HBsAg and presence of anti-HBc (with or without anti-HBs), do not need antiviral therapy, but may need to be monitored during immunosuppressive therapy and considered for prophylactic therapy.

For patients on immunosuppressive medications, HBV reactivation is an important concern and may manifest in many ways, from a subtle change in serum aminotransferase levels to fulminant hepatic failure and death. HBV reactivation has been observed frequently in patients undergoing chemotherapy, with almost half of cases of abnormal liver tests in patients undergoing chemotherapy for hematologic malignancies attributable to HBV reactivation.[5,6] Mortality from fulminant liver failure from HBV reactivation in patients receiving chemotherapy is reported from 4%–60%.[5] Frequency of HBV reactivation is dependent on the type of immunosuppression and state of HBV infection when chemotherapy is given. Cytotoxic chemotherapy for hematologic malignancies appears to carry the greatest risk of HBV

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TABLE 1. Definitions of HBV Infection

	HBsAg	Anti-HBs	Anti-HBc	HBV DNA		ALT/AST	Liver biopsy
				HBeAg (+)	*HBeAg (−)*		
Chronic HBV	Positive	Negative	Positive	>20,000 IU/ml	>2,000 IU/ml	Elevated	Chronic hepatitis with Necroinflammation
Inactive HBV carrier	Positive	Negative	Positive	<20,000 IU/ml	<2,000 IU/ml	Normal	No significant hepatitis
Resolved HBV	Negative	Positive	Positive	Undetectable	Undetectable	Normal	No significant hepatitis

reactivation. Spontaneous reactivation may occur in up to 22% of inactive HBV carriers, with an increase of up to 60% of patients with HBV reactivation with cytotoxic chemotherapy for lymphoma.[5,7] Approximately 40% of inactive HBV carriers may reactivate with chemotherapy for solid tumors.[5,8] Chemotherapeutic regimens including glucocorticoids appear to have the highest risk of HBV reactivation.[6,7]

Factors Unique to IBD

The prevalence of HBV exposure in persons with IBD has been reported in several European studies and one South American study.[9–12] In a study in Italy, evidence of exposure to HBV by hepatitis B core antibody (anti-HBc) was present in 10.9% of CD patients compared to 5.1% of controls ($P = 0.016$).[9] Similarly, 11.5% of UC patients were anti-HBc positive, statistically significantly higher than controls ($P = 0.02$).[9] In Brazil, anti-HBc was found in 17% of IBD patients.[12] In contrast, two recent studies in France and Spain reported HBV exposure rates in IBD patients to be similar to that of the general population.[11,13] In France, anti-HBc was reported in only 2.78% of CD patients and 1.59% of UC patients, similar to that of the general population.[13] In Spain, anti-HBc was reported in 7.1% of CD and 8% of UC patients, similar to that of the general population in Spain.[11] The increased risk of viral hepatitis in IBD patients has been associated with receiving blood transfusions (odds ratio [OR] 2.66–7.77) and possibly surgery.[10,11] The decreasing prevalence of viral hepatitis in IBD patients in recent reports from Spain and France suggest preventative measures such as vaccination and blood supply screening are effective.

Reactivation of HBV is an important concern in patients on immunosuppressive therapy for IBD, but the degree to which it occurs is unknown. The current literature consists primarily of case reports and case series. There are several case reports of HBV reactivation after use of infliximab in combination with prednisone and/or azathioprine.[14–20] Tumor necrosis factor alpha (TNF-α) is important in regulating HBV viral replication.[21,22] There are no case reports of HBV reactivation with adalimumab or certolizumab pegol; however, they are newer TNF-α antagonist medications and HBV reactivation risk would be expected to be a class effect. HBV reactivation may occur with other agents as well. There is one case report of HBV reactivation in a patient with CD treated with metronidazole and mesalamine,[16] and one case report of HBV reactivation in a patient with UC treated with prednisone and azathioprine resulting in fulminant hepatic failure requiring liver transplantation.[23] It is not known if TNF-α antagonists or immunomodulator medications used in IBD carry the same risk of HBV reactivation as cytotoxic chemotherapy. Until further studies on the safety of IBD medications and risk of HBV reactivation in IBD patients are performed, we recommend screening of all IBD patients for prior HBV exposure. This recommendation is based on: 1) increased prevalence of HBV in IBD patients; 2) the potential fatal consequences of HBV reactivation; and 3) the availability of safe and effective anti-HBV drugs to prevent reactivation. This also provides an opportunity to vaccinate patients who lack evidence of prior exposure.

Screening Recommendations

Current guidelines by the American Association for the Study of Liver Diseases (AASLD) and Centers for Disease Control (CDC) recommend HBV screening for populations with intermediate or high prevalence (>2%) and those requiring immunosuppression, which includes patients with IBD[4] (Table 2). Screening for HBV should be performed at the time of diagnosis of IBD rather than delaying until consideration of immunomodulator or TNF-α antagonist medication. HBsAg and hepatitis B surface antibody (anti-HBs) are recommended screening tests.

The utility of hepatitis B core antibody (anti-HBc) to the screening panel is controversial; however, we recommend screening all IBD patients for anti-HBc. Even though anti-HBc may be falsely elevated in a low prevalence population, a positive anti-HBc (in the setting of undetectable HBsAg) can represent chronic HBV in immunosuppressed patients or patients coinfected with HCV or human immunodeficiency virus (HIV).[4,24] There are several reported cases of HBV reactivation in anti-HBs positive and anti-HBc positive patients who underwent bone marrow transplantation or

TABLE 2. Guidelines for HBV Screening

CDC Guidelines (2008)[2]	AASLD Guidelines (2009)[4]
Persons born in geographic regions with HBsAg prevalence of =2%	Individuals born in areas of high (>8%) or intermediate (2-7%) prevalence rates for HBV including immigrants and adopted children
US born persons not vaccinated as infants whose parents were born in geographic regions with HBsAg prevalence of ≥8%	U.S. born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (>8%)
Household contacts and sex partners of HBV-infected persons	Household and sexual contacts of HBsAg (+) persons
Injection-drug users	Persons who have ever injected drugs
Men who have sex with men	Men who have sex with men
Persons with elevated ALT/AST of unknown etiology	Individuals with chronically elevated ALT or AST
Persons with selected medical conditions who require immunosuppressive therapy	Persons with multiple sexual partners or history of sexually transmitted disease
Pregnant women	All pregnant women
Persons infected with HIV	Individuals infected with HCV or HIV
Infants born to HBsAg-positive mothers	Patients undergoing renal dialysis
Persons who are the source of blood or body fluid exposures that might warrant postexposure prophylaxis (e.g., needlestick injury to a healthcare worker)	Inmates of correctional facilities
	Persons needing immunosuppresion

cytotoxic chemotherapy for lymphoma.[25,26] Palmore et al[25] reported six patients who were either anti-HBs-positive and/or anti-HBc-positive with HBV reactivation. All six patients were HBsAg-negative prior to treatment. Five of the six patients had hematologic disorders and one patient had HIV. Four of the six patients died as a result of HBV reactivation. Hui et al[26] reviewed 244 consecutive HBsAg-negative patients with lymphoma treated with chemotherapy and identified eight cases of de novo HBV-related hepatitis which were confirmed to be a reactivation of occult HBV by sequencing. There are no reports thus far of HBV reactivation in IBD patients with anti-HBc and negative HBsAg.

For patients who are positive for HBsAg, anti-HBs, or anti-HBc, follow-up of serum aminotransferase levels and HBV DNA levels is necessary. An algorithm for screening, prophylaxis, and treatment is shown in Figure 1.

Prophylaxis to Prevent Reactivation

Patients with HBsAg should be considered for prophylaxis prior to undergoing treatment with any immunosuppressive medication including steroids, immunomodulators, or biologics to prevent HBV reactivation. While there are no data in IBD patients specifically, prophylaxis has been shown to be beneficial in patients undergoing chemotherapy. A meta-analysis of lamivudine for prophylaxis of HBV reactivation in immunosuppressed patients included 21 studies and showed a mortality benefit of lamivudine (OR 0.36; 95% confidence interval [CI] 0.23–0.56).[27] Randomized controlled trials have shown benefit of prophylaxis with lamivudine for HBV reactivation in patients undergoing chemotherapy.[28–30] Jang et al[28] randomized 73 patients with HBV and hepatocellular carcinoma undergoing transarterial chemo-lipoidolization (TACL) to lamivudine prophylaxis or no prophylaxis. Patients in the prophylaxis arm had a statistically lower rate of HBV reactivation compared to placebo: 2.8% versus 29.7%, respectively ($P = 0.002$). Lau et al[29] randomized 30 lymphoma patients with HBV to lamivudine prophylaxis or no prophylaxis before chemotherapy. None of the patients receiving prophylaxis developed HBV reactivation compared to 53% of those in the no prophylaxis group ($P = 0.002$). Hsu et al[30] also showed a benefit of lamivudine prophylaxis in lymphoma patients, with HBV reactivation in 11.5% versus 56% at 12 months in the prophylaxis and no prophylaxis arms, respectively ($P = 0.001$). Currently, HBV prophylaxis is recommended 7 days prior to initiation of chemotherapy and maintained through 6 months to 1 year after completion of chemotherapy as HBV reactivation may occur after chemotherapy is discontinued.

The recommendation of prophylaxis with lamivudine prior to immunosuppressive therapy in IBD patients is extrapolated from the chemotherapy data detailed above. However, immunosuppressive regimens for IBD differ significantly from those used for chemotherapy. First, medications for IBD, aside from prednisone, differ from those used in the chemotherapy trials and it is unknown whether immunomodulatory drugs for IBD are more or less likely to reactivate HBV than chemotherapy regimens. Second, the duration of immunosuppressive therapy for IBD may be indefinite in contrast to defined, finite therapy for treatment of specific cancers, which likely affects both risk of reactivation and

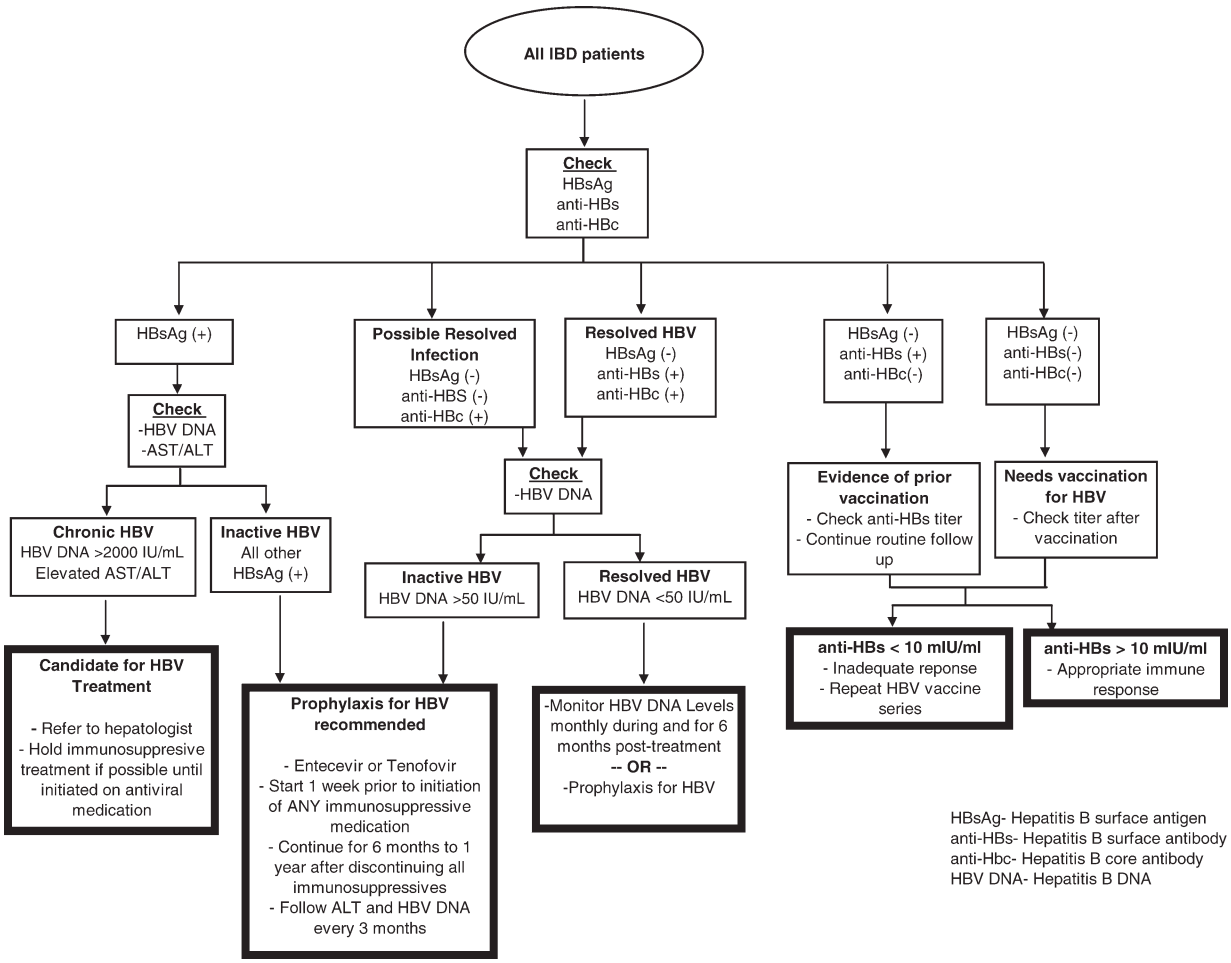

FIGURE 1. An algorithm for the management of viral hepatitis in the patient with inflammatory bowel disease.

risk of prophylactic therapy. Lamivudine, the only medication used in randomized trials for HBV reactivation prophylaxis, is associated with a high rate of drug resistance caused by a single genetic mutation in the tyrosine-methionine-aspartate-aspartate motif (YMDD) of the HBV polymerase.[4] YMDD mutation rates have been reported to be 14%–32% by 1 year and 60%–70% by 5 years of treatment with lamivudine.[4] While lamivudine may be appropriate for a short-duration prophylaxis during chemotherapy, immunosuppressive medications for IBD may be required indefinitely. Alternative antiviral medications for HBV, such as tenofovir, adefovir, telbivudine, and entecavir, have not been evaluated in prophylaxis of HBV reactivation in immunosuppressed patients. However, tenofovir and entecavir have the lowest rates of resistance with long-term use and are the preferred agents for treatment of chronic HBV infection.[4]

Because HBV reactivation may lead to serious or fatal complications, we recommend prophylaxis of HBV reactivation with antiviral medications in appropriate IBD patients who require immunosuppressive medications until further data regarding the efficacy and safety of prophylaxis are available. We recommend the use of tenofovir or entecavir for prophylaxis of HBV reactivation in IBD patients due to lower rates of resistance and excellent safety profiles (Fig. 1). If lamivudine, adefovir, or telbivudine are used, serum aminotransferase levels and HBV DNA levels need to be closely followed to monitor for signs of drug resistance. Esteve et al[17] reported a case of a patient with CD on lamivudine prophylaxis for 5 years who developed lamivudine resistance and was successfully treated with a combination of lamivudine and adefovir with discontinuation of infliximab.

Vaccination to Prevent Infection

HBV infection is a preventable disease. HBV vaccine—a recombinant DNA vaccine given in three injections dosed at 0, 1, and 6 months—is effective in preventing infection. It can be given alone, or in combination with hepatitis A vaccine (hepatitis A discussed below).

Based on several studies, most IBD patients have not been vaccinated. In a survey study, 49% of gastroenterologists never recommended vaccinations for IBD patients.[31] Cross-sectional studies have shown rates of serologic evidence of vaccination for HBV in IBD patients ranging from 12%–49%.[11,13] Age greater than 31 years was a risk factor for nonvaccination (OR 0.29; 95% CI 0.15–0.58; $P = 0.005$).[13]

The timing of HBV vaccination in patients with IBD is important and preferably given prior to initiating therapy with immunomodulators or biologics. In a series of 129 IBD patients who received HBV vaccination, 43% of whom were previously treated or currently receiving immunosuppressive therapy at time of vaccination, 65.9% of patients formed an inadequate response to vaccination, defined as anti-HBs titer of <10 mIU/mL, and 28% of vaccinated patients had no detectable levels of antibodies.[32] Younger patients were observed to be more likely to have an adequate immune response to vaccination. The potential negative effect of immunosuppressive therapy on immune response to vaccination is yet another reason hepatitis screening should occur at diagnosis of IBD prior to initiation of immunosuppressive therapy. Anti-HBs antibody titers should be checked after HBV vaccination in IBD patients, particularly in older patients or patients previously or currently treated with immunosuppressive medications. Patients with an inadequate response (<10 mIU/mL) should receive a second full series of HBV vaccine, as 50% of patients who failed to respond to the initial HBV vaccination series may respond after a second series of three injections.[1] Patients who fail a second series are unlikely to develop adequate immunological response to HBV vaccine.

HEPATITIS C

General Concepts

Unlike chronic HBV infection, which is broadly divided into three categories of disease activity, patients with hepatitis C either have or do not have chronic infection. Exposure to HCV results in chronic infection in over 55%–85% of cases.[2,33] Treatment for HCV is currently recommended for all chronic HCV patients over 18 years of age without a contraindication such as solid organ transplantation (other than liver), uncontrolled depression, autoimmune hepatitis, untreated thyroid disease, pregnancy or inability to comply with contraception, severe concurrent medical disease, age less than 2 years, and known hypersensitivity to anti-HCV medications.[33]

Current optimal therapy for HCV includes pegylated interferon-α and ribavirin. Duration of therapy may vary dependent on viral genotype and initial response, but the majority of patients (genotype 1) will require at least 48 weeks of therapy. Although new antiviral medications against HCV are expected in the near future, they will likely all require pegylated interferon-α as the backbone of therapy.

Factors Unique to IBD

Because HCV is a blood-borne pathogen, IBD patients who underwent surgery or received blood transfusions may be at an increased risk. The blood supply in the United States has been screened for HCV since 1992.[3] The prevalence of HCV exposure in persons with IBD has been reported in several European studies.[9,10,13] In a study in Italy, evidence of prior HCV infection in all age groups by anti-HCV was not significantly higher in CD patients compared to controls (7.4% versus 5.1%, P = NS), and actually lower in UC compared to controls (0.6% versus 5.1%, $P = 0.01$). However, in patients younger than 50 years anti-HCV positivity was more common in CD compared to controls (6.8% versus 1.9%, $P = 0.01$). This age-related trend was not observed in UC patients.[9] In a different Italian study, evidence of prior HCV infection was found in 5.98% of IBD patients.[10] In two recent studies, low rates of prior HCV exposure was detected in IBD patients, although age was not adjusted for in either study.[11,13] In France, anti-HCV was detected in 2.3% of CD patients and 1.3% of UC patients.[13] In Spain, 0.79% of CD patients and 1.59% of UC patients were positive for anti-HCV.[11]

As noted, current optimal therapy for HCV includes pegylated interferon-α and ribavirin. The effect of interferon on IBD is unclear. Several case reports suggest a potential benefit of interferon in UC,[34–36] but other case reports have observed new-onset IBD during interferon treatment or exacerbation of existing IBD with a predominance of UC.[37–43] Tilg et al[44] performed a pilot study using low-dose peginterferon-α2b (0.5–1 μg/kg weekly for 12 weeks) in 60 UC patients with active disease showing no benefit on UC, but no statistically significant increase in adverse reactions. A Cochrane review including three other prospective studies of interferon-α and interferon-β in UC concluded that interferon was not an effective therapy for UC.[45] There were no differences in serious side effects from interferon between treated and untreated patients, but the authors concluded further studies regarding safety were needed. It should be noted that the therapeutic studies investigating interferon as treatment for UC used dosages lower than that used for treatment of HCV, suggesting that a dose effect may partially explain the divergent outcomes reported in the numerous case reports of UC exacerbation with HCV treatment versus the lack of adverse effects observed in low-dose controlled studies of interferon for UC treatment.

If a patient with IBD requires HCV treatment, treatment for HCV appears to be effective. Bargiggia et al[46] performed a case control study of 21 IBD patients with HCV who were treated with non-pegylated interferon-α monotherapy compared to non-IBD HCV controls. Similar efficacy was observed in the IBD and non-IBD controls with sustained viral response (SVR) 24% versus 18% ($P = 0.83$). No difference in adverse events were observed between the IBD and non-IBD controls, nor were exacerbation in gastrointestinal symptoms observed. Scherzer et al[47] prospectively treated 11 patients with HCV and CD with peginterferon-α and ribavirin (one patient with monotherapy peginterferon). Of the 11 patients, five patients (46%) achieved SVR, three (27%) patients relapsed, and three patients (27%) were nonresponders. The efficacy of HCV treatment appeared to be similar to non-IBD patients. Regarding CD medications during HCV treatment, three patients were on azathioprine, four were on mesalamine, one on mycophenolate mofetil, and three on no medications. During HCV treatment 6 of the 11 patients had increased symptoms related to CD and required increased medical therapy with steroids, mesalamine, or antibiotics.[47] Patients with IBD have been excluded from large prospective studies of HCV treatment, so it is difficult to confirm or refute these findings.

Although controlled studies did not identify an increase in risk of UC exacerbation with interferon therapy, case reports of new-onset UC and disease exacerbation highlights the need for further study. The risk–benefit ratio for HCV treatment in patients with IBD needs to be individualized. Ideally, only patients with stable IBD should be considered for HCV treatment, with close monitoring for evidence of exacerbation of IBD symptoms while on treatment.

There are important theoretical concerns with immunosuppressive treatment for IBD in patients with HCV. For example, prednisone, frequently used to treat acute exacerbations, may negatively affect HCV infection by increasing viral replication, a phenomenon observed in the postliver-transplant population. No studies have directly addressed the effect of prednisone on HCV patients with IBD. A case report described two patients (non-IBD) who received prednisone early after SVR with subsequent relapse of HCV.[48] This suggests prednisone should be used with caution immediately after treatment of HCV for concern of HCV relapse. With the availability of steroid-sparing medications for IBD, it may be in the best interest for both IBD and HCV patients to avoid the use of prednisone when possible.

Infliximab, certolizumab pegol, and adalimumab reduce inflammation through TNF-α inhibition. TNF-α may play a role in the pathogenesis of HCV. Elevated TNF-α levels are a negative predictor for response to HCV treatment, so inhibition of TNF-α may be potentially beneficial in HCV.[49] Etanercept was evaluated in a randomized control trial suggesting a benefit as an adjunct therapy with interferon and ribavirin for HCV.[50] No studies have been performed to evaluate the safety of TNF-α antagonist medications in IBD patients with HCV outside of case reports.[51] In patients with rheumatoid arthritis (RA), the use of TNF-α antagonist medication is somewhat more extensive. A case series of 24 RA patients with HCV treated with TNF-α antagonists (21 patients with etanercept, three patients with infliximab) showed no adverse effect of liver enzymes or HCV viral load.[52] In a randomized control trial of etanercept as an adjunct treatment for HCV, adverse events were less common in the etanercept arm compared to placebo.[50] Etanercept is not used for IBD, but its apparent lack of harm in HCV suggests other TNF-α antagonist medications may also be low risk. Presently, there are no data to suggest TNF-α antagonist medications are unsafe in IBD patients with HCV; however, long-term studies are needed.

There are no data on the safety of immunomodulators in HCV among IBD patients. Azathioprine, mycophenolate mofetil, and cyclosporine have been used in HCV patients in the post transplant setting and have shown potential anti-HCV activity.[53–55] The use of immunomodulators in IBD patients with HCV appears to be low risk, although long-term safety studies are needed.

Screening Recommendations

AASLD guidelines for screening for HCV include: persons with a history of illicit drug use, persons with HIV, hemophilia, or on hemodialysis, persons who have received blood transfusion or organ transplantation prior to 1992, children born of HCV-infected mothers, and persons who are current sexual partners of HCV-infected persons.[32] There are no specific recommendations regarding screening for HCV in IBD patients. There is little evidence to suggest treatment for IBD may negatively affect HCV status. Conversely, several therapies for IBD may have antiviral properties. Unfortunately, there is currently no vaccine for HCV.

HEPATITIS A

Hepatitis A virus (HAV) infection is an acute infection transmitted by fecal-oral contamination or direct blood or body fluid contact. Unlike HBV and HCV, HAV does not result in a chronic infection. However, acute infection can be severe or fatal. HAV is common, with an estimated 25,000 cases of acute HAV in the U.S. in 2007 with up to 33.5% of the U.S. population infected in the past.[2] While acute HAV has not been reported to have any specific negative outcomes in patients with IBD, it is a preventable infectious disease.

HAV vaccine is available separately or packaged together with the HBV vaccine as a single injection. HAV vaccine is an inactivated live virus and requires a primary vaccination injection followed by a booster injection, separated by 6–12 months. Protection develops 2–4 weeks after primary vaccination, with over 94%–100% of patients developing neutralizing antibodies by 1 month, although patients on immunosuppressive medications may have a lower immunologic response.[2] Neutralizing antibodies persist up to 8 years, and completion of HAV vaccination series presumably provides lifelong protection. The HAV and HBV combination vaccine is also dosed at 0, 1, and 6 months with comparable efficacy.

We recommend all IBD patients should be considered for vaccination against HAV, as they may be at increased risk of severe HAV infection, particularly if immunosuppressed. Although the HAV vaccine is an inactivated virus, we recommend IBD patients be vaccinated prior to initiation of immunosuppressive medications to increase the probability of immunologic response.

CONCLUSIONS

Viral hepatitis is common worldwide and in the U.S. As IBD patients are at risk for requiring immunosuppressive medications, all IBD patients should be screened for HBV. AASLD guidelines recommend screening with HBsAg and anti-HBs. We also consider screening with anti-HBc to detect occult HBV. IBD patients with evidence of active chronic HBV (elevated liver tests and HBV DNA levels) should receive HBV treatment. Although data for IBD and risk of HBV reactivation are lacking, based on oncologic data we recommend prophylaxis prior to initiation of any immunosuppressive therapy in all patients who are HBsAg-positive, regardless of HBV DNA level. Patients with positive anti-HBc without HBsAg and undetectable viral DNA should be monitored closely for reactivation. Chronic HCV disease does not appear to be affected by IBD medications, although few data exist in IBD patients. HCV treatment with peg-interferon and ribavirin may exacerbate gastrointestinal symptoms, and therefore the decision to treat HCV needs to be individualized. More studies specifically in IBD patient with HBV and HCV are needed. We recommend vaccination against HBV and HAV in all patients who have not been exposed or already immunized.

REFERENCES

1. World Health Organization. Immunization, vaccines and biologicals, hepatitis B. Available at: http://www.who.int/immunization/topics/hepatitis_b/en/index.html Accessed November 11, 2008.
2. Centers for Disease Control http://www.cdc.gov/hepatitis/statistics.htm
3. [No authors listed.] NIH Consensus Statement on Management of Hepatitis C. *NIH Consens State Sci Statements*. 2002;19:1–46.
4. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50:661–662.
5. Kohrt HE, Ouyang DL, Keeffe EB. Antiviral prophylaxis for chemotherapy-induced reactivation of chronic hepatitis B virus infection. *Clin Liver Dis*. 2007;11:965–991, x.
6. Yeo W, Chan PK, Zhong S, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol*. 2000;62:299–307.
7. Lok AS, Liang RH, Chiu EK, et al. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. *Gastroenterology*. 1991;100:182–188.
8. Yeo W, Chan PK, Hui P, et al. Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a prospective study. *J Med Virol*. 2003;70:553–561.
9. Biancone L, Pavia M, Del Vecchio Blanco G, et al., Italian Group for the Study of the Colon and Rectum (GISC). Hepatitis B and C virus infection in Crohn's disease. *Inflamm Bowel Dis*. 2001;7:287–294.
10. Longo F, Hebuterne X, Tran A, et al. Prevalence of hepatitis C in patients with chronic inflammatory bowel disease in the region of Nice and evaluation of risk factors. *Gastroenterol Clin Biol*. 2000;24:77–81.
11. Loras C, Saro C, Gonzalez-Huix F, et al., GETECCu (Grupo Español de Enfermedades de Crohn y Colitis Ulcerosa). Prevalence and factors related to hepatitis B and C in inflammatory bowel disease patients in Spain: a nationwide, multicenter study. *Am J Gastroenterol*. 2009;104:57–63.
12. Tolentino YF, Fogaca HS, Zaltman C, et al. Hepatitis B virus prevalence and transmission risk factors in inflammatory bowel disease patients at Clementino Fraga Filho university hospital. *World J Gastroenterol*. 2008;14:3201–3206.
13. Chevaux JB, Bigard MA, Bensenane M, et al. Inflammatory bowel disease and hepatitis B and C. *Gastroenterol Clin Biol*. 2009 [Epub ahead of print].
14. Millonig G, Kern M, Ludwiczek O, et al. Subfulminant hepatitis B after infliximab in Crohn's disease: need for HBV-screening? *World J Gastroenterol*. 2006;12:974–976.
15. Colbert C, Chavarria A, Berkelhammer C. Fulminant hepatic failure in chronic hepatitis B on withdrawal of corticosteroids, azathioprine and infliximab for Crohn's disease. *Inflamm Bowel Dis*. 2007;13:1453–1454.
16. Esteve M, Loras C, González-Huix F. Lamivudine resistance and exacerbation of hepatitis B in infliximab-treated Crohn's disease patient. *Inflamm Bowel Dis*. 2007;13:1450–1451.
17. Esteve M, Saro C, González-Huix F, et al. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut*. 2004;53:1363–1365.
18. Madonia S, Orlando A, Scimeca D, et al. Occult hepatitis B and infliximab-induced HBV reactivation. *Inflamm Bowel Dis*. 2007;13:508–509.
19. Ojiro K, Naganuma M, Ebinuma H, et al. Reactivation of hepatitis B in a patient with Crohn's disease treated using infliximab. *J Gastroenterol*. 2008;43:397–401.
20. Ueno Y, Tanaka S, Shimamoto M, et al. Infliximab therapy for Crohn's disease in a patient with chronic hepatitis B. *Dig Dis Sci*. 2005;50:163–166.
21. Yoshioka K, Kakumu S, Arao M, et al. Immunohistochemical studies of intrahepatic tumour necrosis factor alpha in chronic liver disease. *J Clin Pathol*. 1990;43:298–302.
22. Kim YJ, Lee HS, Yoon JH, et al. Association of TNF-alpha promoter polymorphisms with the clearance of hepatitis B virus infection. *Hum Mol Genet*. 2003;12:2541–2546.
23. Zeitz J, Mullhaupt B, Fruehauf H, et al. Hepatic failure due to hepatitis B reactivation in a patient with ulcerative colitis treated with prednisone. *Hepatology*. 2009;50:653–654.
24. Gandhi RT, Wurcel A, Lee H, et al. Isolated antibody to hepatitis B core antigen in human immunodeficiency virus type-1-infected individuals. *Clin Infect Dis*. 2003;36:1602–1605. Erratum: Clin Infect Dis 2003;37:157.
25. Palmore TN, Shah NL, Loomba R, et al. Reactivation of hepatitis B with reappearance of hepatitis B surface antigen after chemotherapy

and immunosuppression. *Clin Gastroenterol Hepatol*. 2009;7:1130–1137.
26. Hui CK, Cheung WW, Zhang HY, et al. Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. *Gastroenterology*. 2006;131:59–68.
27. Katz LH, Fraser A, Gafter-Gvili A, et al. Lamivudine prevents reactivation of hepatitis B and reduces mortality in immunosuppressed patients: systematic review and meta-analysis. *J Viral Hepat*. 2008;15:89–102.
28. Jang JW, Choi JY, Bae SH, et al. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. *Hepatology*. 2006;43:233–240.
29. Lau GK, Yiu HH, Fong DY, et al. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. *Gastroenterology*. 2003;125:1742–1749.
30. Hsu C, Hsiung CA, Su IJ, et al. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. *Hepatology*. 2008;47:844–853.
31. Gupta A, Macrae FA, Gibson PR. Vaccination and screening for infections in patients with inflammatory bowel disease: a survey of Australian gastroenterologists. *Intern Med J*. 2009 [Epub ahead of print].
32. Vida Pérez L, Gómez Camacho F, García Sánchez V, et al. Adequate rate of response to hepatitis B virus vaccination in patients with inflammatory bowel disease. *Med Clin (Barc)*. 2009;132:331–335.
33. Ghany MG, Strader DB, Thomas DL, et al., American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49:1335–1374.
34. Sümer N, Palabiyikoðlu M. Induction of remission by interferon-alpha in patients with chronic active ulcerative colitis. *Eur J Gastroenterol Hepatol*. 1995;7:597–602.
35. Musch E, Andus T, Malek M. Induction and maintenance of clinical remission by interferon-beta in patients with steroid-refractory active ulcerative colitis-an open long-term pilot trial. *Aliment Pharmacol Ther*. 2002;16:1233–1239.
36. Musch E, Andus T, Kruis W, et al. Interferon-beta-1a for the treatment of steroid-refractory ulcerative colitis: a randomized, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol*. 2005;3:581–586.
37. Villa F, Rumi MG, Signorelli C, et al. Onset of inflammatory bowel diseases during combined alpha-interferon and ribavirin therapy for chronic hepatitis C: report of two cases. *Eur J Gastroenterol Hepatol*. 2005;17:1243–1245.
38. Morimoto K, Yamagami H, Hosomi S, et al. Development of pouchitis with combination therapy with peg-interferon alpha-2b and ribavirin for chronic hepatitis C in a patient with ulcerative colitis who underwent pouch surgery. *Am J Gastroenterol*. 2009;104:1609–1610.
39. Watanabe T, Inoue M, Harada K, et al. A case of exacerbation of ulcerative colitis induced by combination therapy with PEG-interferon alpha-2b and ribavirin. *Gut*. 2006;55:1682–1683.
40. Sprenger R, Sagmeister M, Offner F. Acute ulcerative colitis during successful interferon/ribavirin treatment for chronic hepatitis. *Gut*. 2005;54:438–439.
41. Tursi A. Rapid onset of ulcerative colitis after treatment with PEG-interferon plus ribavirin for chronic hepatitis C. *Inflamm Bowel Dis*. 2007;13:1189–1190.
42. Mavrogiannis C, Papanikolaou IS, Elefsiniotis IS, et al. Ulcerative colitis associated with interferon treatment for chronic hepatitis C. *J Hepatol*. 2001;34:964–965.
43. Khalil A, Lucidarme D, Desurmont P, et al. Crohn's disease associated with interferon and ribavirin treatment for chronic hepatitis C. *Gastroenterol Clin Biol*. 2005;29:193–196.
44. Tilg H, Vogelsang H, Ludwiczek O, et al. A randomised placebo controlled trial of pegylated interferon alpha in active ulcerative colitis. *Gut*. 2003;52:1728–1733.
45. Seow CH, Benchimol EI, Griffiths AM, et al. Type I interferons for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2008;:CD006790.
46. Bargiggia S, Thorburn D, Anderloni A, et al. Is interferon-alpha therapy safe and effective for patients with chronic hepatitis C and inflammatory bowel disease? A case-control study. *Aliment Pharmacol Ther*. 2005;22:209–215.
47. Scherzer TM, Staufer K, Novacek G, et al. Efficacy and safety of antiviral therapy in patients with Crohn's disease and chronic hepatitis C. *Aliment Pharmacol Ther*. 2008;28:742–748.
48. Lin A, Thadareddy A, Goldstein MJ, et al. Immune suppression leading to hepatitis C virus re-emergence after sustained virological response. *J Med Virol*. 2008;80:1720–1722.
49. Fukuda R, Ishimura N, Ishihara S, et al. Intrahepatic expression of pro-inflammatory cytokine mRNAs and interferon efficacy in chronic hepatitis C. *Liver*. 1996;16:390–399.
50. Zein NN; Etanercept Study Group. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. *J Hepatol*. 2005;42:315–322.
51. Campbell S, Ghosh S. Infliximab therapy for Crohn's disease in the presence of chronic hepatitis C infection. *Eur J Gastroenterol Hepatol*. 2001;13:191–192.
52. Peterson JR, Hsu FC, Simkin PA, et al. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. *Ann Rheum Dis*. 2003;62:1078–1078.
53. Schiavon LL, Carvalho-Filho RJ, Narciso-Schiavon JL, et al. Impact of cyclosporine-based immunosuppressive therapy on liver histology of hepatitis C virus-infected renal transplant patients. *Hepatology*. 2008;48:348–349.
54. Samonakis DN, Triantos CK, Thalheimer U, et al. Immunosuppression and donor age with respect to severity of HCV recurrence after liver transplantation. *Liver Transpl*. 2005;11:386–395.
55. Zekry A, Gleeson M, Guney S, et al. A prospective cross-over study comparing the effect of mycophenolate versus azathioprine on allograft function and viral load in liver transplant recipients with recurrent chronic HCV infection. *Liver Transpl*. 2004;10:52–57.