Hepatitis B Reactivation during Immunosuppression: From Pathogenesis to Management Strategy

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Abstract

Hepatitis B is one of the most common viral hepatitis that poses significant health risks in immunocompetent and more so in immunocompromised patients. Increasing scientific development and research in the fields of various autoimmune diseases and oncology have led to the evolution of several chemotherapy agents and newer modalities of treatment of these entities resulting in profound immunomodulation or immunosuppression. In the current era of under-diagnozed or under-screened population for hepatitis B, there is potential risk of developing severe or fulminant hepatitis B if such patients are exposed to immunosuppressive agents. This paper outlines the pathophysiology, clinical outcomes and explores the risk factors for hepatitis B reactivation during immunosuppression. Additionally we also propose a simplistic algorithm for the management of hepatitis B reactivation during immunosuppression that can be adopted by physicians taking care of such patients.

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Introduction

Hepatitis B is found to have infected at least one third of the world's population and approximately 370 million people worldwide are chronic hepatitis B virus (HBV) carriers. Although the incidence of hepatitis B infection are declining after the advent of universal vaccination in USA, immigration from endemic areas and high risk life styles still account for new cases. Chronic HBV infection could have significant mortality and morbidity from the long term complications like cirrhosis or hepatocellular carcinoma[1] Reactivation of hepatitis B is a well documented phenomenon and can practically occur in any immunosuppressed state including that induced by pharmacologic agents such as chemotherapy drugs, disease modifying anti-rheumatic drugs (DMARDS), or immune modulators.[2,3] Recently, increasing use of agents like corticosteroids, biologic agents including tumor necrosis factor-alfa inhibitors, potent post transplant immunosuppressive agents in managing different disease stages have also been implicated in hepatitis B reactivation resulting in mild to severe flares of hepatitis.[4] Although majority of the patients experience a mild asymptomatic elevation of transaminases, serious complications like icteric hepatitis, fulminant liver failure either leading to liver transplantation or death have been reported.[5,6] Overall hepatitis B reactivation ranges from 14 to 72% of HBsAg+ carriers with more than 48% cases after chemotherapy for lymphoma or hematologic disease[7,8] and about 15% after chemotherapy for solid organ tumors, although the latter is less well established.[9]

Pathogenesis and Clinical Outcomes

The natural history of HBV infection depends upon the age at which the infection was acquired but the majority of clinical outcomes including viral clearance are contingent upon the host immunity, which can present in one of the following phases or stages: immunotolerance, immunoclearance, inactive carrier, reactivation phase. Having immune control on HBV replication during the above phases can result in very low level of HBV viral replication and undetectable HBsAg with detectable HBsAb. Such stage is considered as serologic resolved hepatitis B infection. HBV is generally not cytopathic and the liver injury in HBV infection is often from immue mediated necroinflammation. Host immunity can be variable depending on the presentation of viral epitopes to CD8+ T lymphocytes and subsequent recruitment of CD4+ T lymphocytes leading to cellular and immune mediated hepatocyte destruction.[10,11] Non-cytopathic pathways of viral

control can be exerted by local cytokines, interferon gamma and TNF alfa cytokines.[12,13,14] HBV reactivation is referred to those who have achieved the status of inactive carrier or serologic resolved HBV infection, then reverse their status and become active HBV infection with significant viral replication and often elevated transaminases. A phenomenon called reverse- seroconversion is often observed during CHB reactivation. A common scenario is that patient with HBsAg-/ HBsAb+/- and HBcAb+ before chemotherapy but presented with positive HBsAg and increase viral replication during or after chemotherapy.[15,16,17] Since the host immunity plays a major role in the disease manifestation, the flucturation on the level of host immunity mediated the immunosuppressant is setting the stage for more rapid and extensive immune reaction.

In clinical practice, immunosuppression with steroids, chemotherapy or biologic agents is given intermittently in majority of the cases in order to prevent toxicity due to continuous exposure to the agent. Among chronic HBV carriers, the virus often gets reactivated and replicates during the immunosuppressed state resulting in an increase in the viral load. The host immunity is restored upon withdrawal of the agent, which leads to immune mediated damage of the hepatitis b infected hepatocytes that can lead to severe hepatitis flares and even rapidly progressing fulminant liver failure. Viral replication after the start of chemotherapy is primarily due to loss of immune control over the virus but there is also some evidence to support that intensive immunosuppression especially involving steroid therapy can be directly stimulate the steroid responsive genome of the virus thus leading to enhanced viral replication.[18]

Clinical outcomes can range from mild to severe flares depending on the viral factors and the intensity of host immunosuppression. Majority of the reactivation of hepatitis B remain mild with asymptomatic elevation of the transaminases. Severe flares leading to icteric hepatitis, fulminant failures resulting in liver transplantation or death are mostly observed in HBV reactivation among those patients with lymphoma and c or during chemotherapy for hematologic diseases.[19,20] CHOP regimen for lymphoma has been showed to cause hepatitis B reactivation in 38-48% of HBsAg+ cases. In one study more 23% of the HBsAg+ cases developed severe hepatitis, 74% developed fulminant failure of which half of them expired subsequently.[19] Rituximab is a monoclonal antibody to CD20, It can deplete the entire host B Cells when the drup is administered. Rituximab has shown to cause serious flares in HBsAg+ viremic patients and also accounted for the majority of the cases with reverse seroconversion on HBeAb or HBeAb status.[21,22,23] Risk of reactivation is over 50% in post hematopoetic stem cell transplant and reaches 70% by 5th year post transplant that correlates with a declining HBsAb titer. The risk of reactivation is higher when there is occurrence of GVHD post stem cell transplant which is usually requiring intensive chemotherapy. Chemotherapy for solid organ tumors such as breast, pancreas, liver, nasopharyngeal cancer can have a reactivation rate ranging from 15-50%. However, the data is limited and less well established.[9,24]

Poorer outcomes occur not only due to liver related complications but also due to delay or interruption of the subsequent chemotherapy in the setting of the flare. About 70% of the patients in one study could not adhere to the scheduled chemotherapy regimen due to the flares.[25] This can result in poorer outcomes that's not only cancer related but also due to progression of the ongoing hepatitis flare as it is difficult to control once the flare has been initiated.

Management Strategy

Identify the Risk Factors

Host factors: Patients with pre-existing liver disease, unrecognized cirrhosis or advanced fibrosis are probably the most important group that has the highest burden or worse outcome from HBV reactivation. Extremes of age probably due to decreased physiologic reserve and those who are HBsAb negative are other risk factors for poorer outcome after reactivation. In stem cell transplant situations donor+, recipient+ has the highest risk of HBV reactivation than donor+, recipient- than donor-, recipient+ than both negative.[26,27]

Viral factors: Although there is no single predictor, a few viral factors have been found to reliably predict the severity of reactivation of hepatitis B. In inactive carrier who has HBsAg positive but low viral load or undetectable DNA level, the reactivation rate in the setting of immunosuppression is variable and depends on the type of immunosuppressant.[28] Besides HBsAg positivity, HBeAg positivity, or/and high viral load prior to chemotherapy account as the strongest predictor of HBV reactivation after the initiation of chemotherapy.[29] Occult HBV infection is a unique clinical entity, which characterized by HBsAg-, HBsAb +/- but positive HBV DNA, is also at risk of reactivation about 1-5% as evidenced in two series of post chemotherapy for hematologic disease and post kidney transplant.[30,31] The risk of reactivation is lower for isolated HBcAb+ but few case reports of reactivation do exist in such a scenario due to reverse-seroconversion.[19,20,32] There are also published reports of HBV reactivation in cases with HBcAb+ and HBsAb+ prior to chemotherapy. The use of more than one chemotherapeutic agent and HBsAb titers less than 100 IU/ L were the probable risk factors for such a reactivation.[51] Although more data is warranted, reverse-seroconversion appears to occur even in the presence of HBsAb when stronger immunosuppression is administered.

Pharmacologic factors: Various immunomodulatory agents have been linked to HBV reactivation. Although it is difficult to define a minimal level for immunosuppression at which the risk HBV reactivation is absent, short course of low dose steroids or DMARDs like hydroxychloroquine, sulfasalazine, have probable lower risk of HBV reactivation in low risk individuals.[33] However presence of other immunosuppressed states like renal failure, congestive heart failure may enhance

the risk of reactivation on these agents. Other DMARDs like leflunomide, etanercept, methotrexate, cyclosporine and biologic agents like tumor necrosis factor alfa inhibitors (infliximab, adalimumab, certolizumab, natalizumab) have been reported to cause dramatic icteric flares due to HBV, which led to liver transplantation and death.[34,35,36] Chemotherapy agents involving steroids and B cell depleting agents like rituximab have the strongest potential to reactivate HBV.[21,37,38]

Screening for HBV Infection

As there is no evidence for cost effectiveness of universal screening and universal vaccination in hepatitis B, high risk individuals should be identified and screened. High risk individuals include those from endemic areas where HBsAg positive prevalence higher than 2%, house hold or sexual contacts with HBV infection, HIV infected patients, those on dialysis, IV drug users and homosexuals. CDC recommends screening for all three serologies including HBcAb, HBsAg and HBsAb in those planned for immunosuppression.[39] HBV DNA is not a good screening test as it does not identify inactive carriers and thus should be performed once HBsAg is positive or if a suspicion of occult HBV infection exists. According to the guidelines of American College of Rheumatology, screening is also recommended for all the patients before DMARD therapy. Thus identifying high risk individuals and those about to receive high risk therapy should undergo stringent screening for HBV.

Table 1. Candidates for screening based on cdc recommendation.

CANDIDATES FOR SCREENING BASED ON CDC RECOMMENDATION
— Persons from endemic areas of hepatitis B
— Household and sexual contacts of HBsAg-positive persons
— Persons who have ever injected drugs*
— Persons with multiple sexual partners or history of sexually transmitted disease
— Men who have sex with men
— Inmates of correctional facilities
— Individuals with chronically elevated ALT or AST
— Individuals infected with HCV or HIV
— Patients undergoing renal dialysis
— All pregnant women

Anti-Viral Prophylaxis or Other Preventive Methods

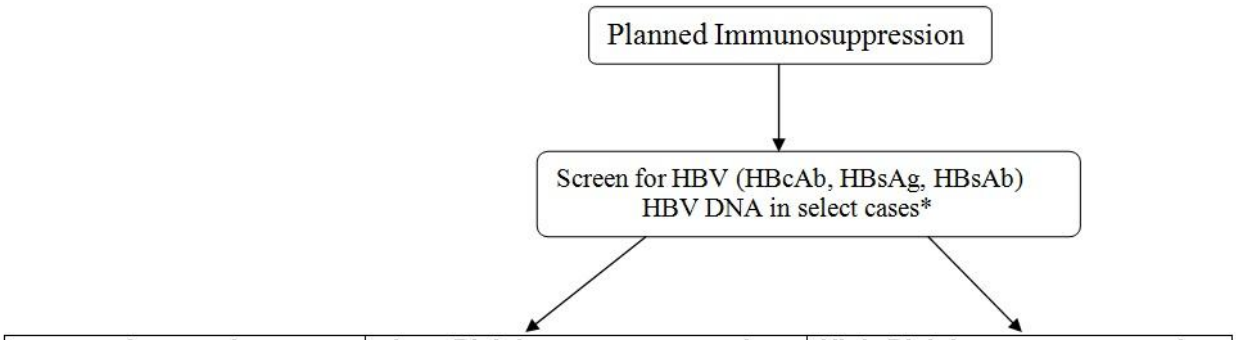
Oral agents like nucleoside and nucleotide analogs are the most favorable modality to prevent HBV reactivation in immunosuppressed states. Lamivudine is the agent with most evidence but other agents like Adefovir, Entecavir and Tenofovir have also been used successfully as prophylaxis for HBV reactivation, although larger studies are still awaited.[40,41] The choice and duration of treatment should preferably be individualized and evaluated to minimize potential risk of toxicities due to the drug. The oral agent of choice should be initiated at least 1 week prior to the start of immunosuppression and should be continued at least for 6months after chemotherapy if patient seroconverts or if the case has isolated HBcAb+.[7,20,32] In all other cases treatment should be continued until HBsAg seroconversion in order to prevent HBV flare after discontinuation. In HBsAb-negative patients, HBV vaccine can be administered prior to immunosuppression to achieve optimal HBsAb titers, however on several occasions immunosuppression or chemotherapy cannot wait that long for sufficient vaccine response. A significantly decreased response rate ranging from 5-15% is seen post HBV vaccine in immunocompromised and post transplant patients.[42,43] Thus CDC recommends a higher dose of recombinant vaccine (40 micrograms) be given on 0, 1, 2 and 6-month schedules.[39]

Earlier studies have shown that HBsAb stem cell transplant donors can impart adaptive immunity to the hepatitis b recipient and help in HBV clearance. The response is stronger in donors who acquired HBsAb after natural infection than those who acquired after immunization. However stem cell transplant is associated with higher toxicity and cannot be feasible universally.[44,45]

Interferon alfa has also been tried in the setting of HBV reactivation during chemotherapy but the treatment has not been advocated due to increased toxicity from interferon and chemotherapy. Also inadequate responses have been noted in Asian population and the therapy might not achieve HBsAg seroconversion given the short time before chemotherapy. Concern also exists regarding bone marrow toxicity in transplant setting and the progression or enhancement of the flare severity due to interferon.[46,47]

HBIG has been tried in several situations, but its routine use is currently in vogue after liver transplantation. Even in the setting of post liver transplantation, recent studies have suggested successful efficacy of low dose intramuscular HBIG and a trend to substitute it with the newer potent anti viral agents.[50] The intramuscular injections of HBIG after stem cell transplantation has fallen out of favor due to the occurrence of injection site hematomas in such thrombocytopenic patients. There is insufficient data regarding HBIG use in other immunosuppression settings.[48,49]

Figure 1. Algorithm for HBV Prophylaxis in Immunosuppression.



Approach	Low Risk Immunosuppression (Prednisone <7.5mg/day or equivalent)	High Risk Immunosuppression (Prednisone>7.5mg/day or equivalent)
HBcAb-, HBsAg-, HBsAb-	Consider HBV vaccine	Consider HBV Vaccine
Isolated HBcAb+	Monitor HBV DNA, LFTs	Start antiviral prophylaxis
HBcAb+, HBsAb+	Monitor HBV DNA, LFTs	Start antiviral prophylaxis
HBsAg+, HBV DNA-	Consider antiviral prophylaxis	Start antiviral prophylaxis
HBsAg+, HBV DNA+	Start antiviral prophylaxis	Start antiviral prophylaxis

*if stigmata of HBsAg mutants or severe immunoglobulin deficiency exists

Summary and Future Direction

Several factors have been showed to contribute to hepatitis B reactivation. Hepatitis B reactivation is the consequence of the changing dynamic between the host and viral factors due to immunosuppression, which is induced by pharmacology agents. Screening for the evidence of hepatitis B infection in at risk population is the key element to manage patients receiving chemo- or chemo-immune therapy.

Reactivation of chronic hepatitis B infection in patients received immunosuppression therapy is common. Even though there is no reliable method to predict who will remain in disease quiescent and who will reactivate, it has been observed that patients with HBsAg positive with detectable DNA have more frequent reactivation than the other entities. However, isolated HBcAb positive patients can still have diseases reactivation, especially in the setting of lymphoma and patients receiving chemo- or chemo-immune therapy. This entity may include patients with occult HBV infection who may have measurable HBV DNA in the serum or patients with HBsAg mutation leading to negative serology testing for HBsAg. The general consensus for giving prophylaxis to patients with isolated HBcAb positive has not been reached. It is not unreasonable to implementation of HBV reactivation prophylaxis in patients with isolated HBcAb positive and measurable serum DNA or even in HBV DNA negative subjects who are to receive prolonged and efficient immune suppressive interventions of any kind.

Oral antiviral agent, such as lamivudine has been widely used for HBV reactivation prophylaxis. Other modalities have been studied with no clear-cut indication to be used in this setting. In order to be effective, antiviral agent like lamivudine prophylaxis must be initiated before treatment. Due to the effects of rebounds in immune competence upon the latent infection may cause late reactivation of the disease, antiviral therapy must be continued and protracted well beyond the cessation of immune suppressive therapy.

Further research in genomic susceptibility or gene profiling may lead to better selection of candidate to receive HBV reactivation prophylaxis. Viral dynamic including variants during reactivation and the changes in host immunity needs to be further studied, so the timing and duration of the prophylaxis can be better defined. Lastly, researches on how to implement the standard of care in screening hepatitis B among patients receiving chemo or chemo-immune therapy are urgently needed as identifying the candidates is essential, but under screening for hepatitis B is very common in the healthcare provided in the US.

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