INASL Guidelines on Management of Hepatitis B Virus Infection in Patients receiving Chemotherapy, Biologicals, Immunosupressants, or Corticosteroids

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Hepatitis B Virus (HBV) reactivation in patients receiving chemotherapy, biologicals, immunosupressants, or corticosteroids is emerging to be an important cause of morbidity and mortality in patients with current or prior exposure to HBV infection. These patients suffer a dual onslaught of illness: one from the primary disease for which they are receiving the culprit drug that led to HBV reactivation, and the other from HBV reactivation itself. The HBV reactivation not only leads to a compromised liver function, which may culminate into hepatic failure; it also adversely impacts the treatment outcome of the primary illness. Hence, identification of patients at risk of reactivation before starting these drugs, and starting treatment aimed at prevention of HBV reactivation is the best strategy of managing these patients. There are no Indian guidelines on management of HBV infection in patients receiving chemotherapy, biologicals, immunosupressants, or corticosteroids for the treatment of rheumatologic conditions, malignancies, inflammatory bowel disease, dermatologic conditions, or solid-organ or bone marrow transplantation. The Indian National Association for Study of the Liver (INASL) had set up a taskforce on HBV in 2016, with a mandate to develop consensus guidelines for management of various aspects of HBV infection, relevant to India. In 2017 the taskforce had published

Abbreviations: ACLF: Acute-on-Chronic Liver Failure; AFP: Alphafetoprotein; ALT: Alanine Aminotransferase; Anti-HBc: Antibodies to Hepatitis B Core Antigen; Anti-HBs: Antibodies to Hepatitis B Surface Antigen; cccDNA: Covalently Closed Circular Deoxyribonucleic Acid; CHB: Chronic Hepatitis B; CHOP: Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone; CKD: Chronic Kidney Disease; DILI: Drug-Induced Liver Injury; DNA: Deoxyribonucleic Acid; ETV: Entecavir; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; HAV: Hepatitis A Virus; HBcAg: Hepatitis B Core Antigen; HBeAg: Hepatitis B Envelope Antigen; HBIG: Hepatitis B Immune Globulin; HBsAg: Hepatitis B Surface Antigen; HBV DNA: Hepatitis B Virus Deoxyribonucleic Acid; HBV: Hepatitis B Virus; HDV: Hepatitis D Virus; HEV: Hepatitis E Virus; HLA: Human Leukocyte Antigen Class I; INASL: Indian National Association for Study of the Liver; LAM: Lamivudine; NAs: Nucleos(t)ide Analogs; NHL: Non-Hodgkin's Lymphoma; NK: Natural Killer; PegIFN-α: Pegylated Interferon Alpha; RA: Rheumatoid Arthritis; rcDNA: Relaxed-Circular Deoxyribonucleic Acid; SLE: Systemic Lupus Erythematosus; TAF: Tenofovir Alafenamide; TDF: Tenofovir Disoproxil Fumarate; TLC: Total Leucocyte Count; ULN: Upper Limit of Normal

the first INASL guidelines on management of HBV infection in India. In the present guidelines, which are in continuation with the previous guidelines, the issues on management of HBV infection in patients receiving chemotherapy, biologicals, immunosupressants, or corticosteroids are addressed. (J Clin Exp Hepatol 2018;8:403–431)

Chronic Hepatitis B Virus (HBV) infection is one of the significant causes of liver related morbidity and mortality.[1] A recently published pooled analysis estimated that in 2010, globally, about 248 million individuals were Hepatitis B Surface Antigen (HBsAg) positive with a large regional variation.[2] Despite the use of antivirals and vaccines, new HBV infection still remains a problem.[3] In fact the number of HBV related deaths had increased between 1990 and 2013 by 33%.[4] Approximately one-third of the world's population or two billion people have been infected and carry serological evidence of past or present HBV infection.[5]

When subjects with current or prior exposure to HBV infection receive chemotherapy, biologicals, immunosupressants, or steroids for some indication, some of them may develop a reactivation of their HBV infection leading to significant morbidity and mortality. These patients suffer a dual onslaught of illness: one from the primary disease for which they were receiving the culprit drug that led to reactivation, and the other from HBV reactivation itself. The reactivation not only leads to deranged liver function, which may culminate into liver failure; it also adversely impacts the treatment outcome of the primary disease. Thus the best chance of managing these patients is timely identification of patients at risk of reactivation, and treatment aimed at prevention of HBV reactivation.

In managing these patients, the role of clinician is twofold: first to evaluate the patients at risk for reactivation of HBV, and second to diagnose reactivation timely in those who develop liver function abnormalities during the course of the immunosuppressive treatment. Emphasis needs to be placed in the prevention of reactivation by doing appropriate testing as reactivation may lead to decompensation or even fulminant hepatic failure resulting in mortality.[6] There are no Indian guidelines on prevention and management of HBV reactivation in patients receiving chemotherapy, biologicals, immunosupressants, or steroids. The Indian National Association for Study of the Liver (INASL) had set up a taskforce on HBV in 2016, with a mandate to develop consensus guidelines for management of various aspects of HBV infection, relevant to India. In 2017 the taskforce had published the first INASL guidelines on management of HBV infection in India.[1] In the present guidelines, which are in continuation with the previous guidelines, the issues on management of HBV infection in patients receiving chemotherapy, biologicals, immunosupressants, or steroids are addressed. The last section also discusses the management of HBV infection in Chronic Kidney Disease (CKD) patients.

For development of these guidelines, the taskforce first identified contentious issues on the topic of HBV reactivation in patients receiving chemotherapy, biologicals, immunosupressants, or steroids; and these were allotted to individual members of the taskforce who reviewed them in detail. A one-day round table discussion was held on 24th September 2017 at New Delhi, to discuss, debate, and finalize the consensus statements. Only those statements that were unanimously approved by the members of the taskforce were accepted. Each statement of the guideline was graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system with minor modifications[7]. The strength of recommendations (strong: 1, weak: 2) thus reflects the quality (grade) of underlying evidence (A, B, C, D) (Table 1).

BASIC IMMUNOLOGY AND CLINICAL CONSEQUENCES OF HBV REACTIVATION

The Virus Lifecycle

HBV is a hepatotropic DNA virus with an extremely compact genomic organization.[8] The small (3.2 kb), partially double-stranded, Relaxed-Circular DNA (rcDNA) features four overlapping open reading frames that are translated into viral core protein, surface proteins, polymerase/reverse transcriptase, and HBx protein.[9] On entering hepatocytes, the HBV nucleocapsid is transported to the nucleus to release the rcDNA genome which is converted to a Covalently Closed Circular DNA (cccDNA) (Figure 1). The cccDNA along with host's histone forms an episomal chromosome like structure and serves as a transcription template for different viral proteins.[10] In addition to complete infectious virions, the infected cells produce a large excess of genome-free, non-infectious subviral particles of HBsAg. Viral genome integration in the host genome can occur randomly and make the patient more susceptible to develop hepatocellular carcinoma.[11]

Immunopathogenesis of HBV Infection

HBV induces a series of innate[12] and adaptive[13] immune responses. The virus is said to display immense 'stealth and cunning' properties[14] and all viral proteins have the capability to interfere in many of immune responses. Viral clearance in immunocompetent adult involves the induction of a robust adaptive CD8 T cell reaction inducing both a cytolytic-dependent and -independent antiviral effect via the expression of antiviral cytokines, as well as the induction of B cells producing neutralizing antibodies.

Table 1 Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Level of evidence		Confidence in the evidence
High	Data derive d from meta-analyses or systematic reviews or from (multiple) randomized trials with high quality.	Further research is unlikely to change our confidence in the estimate of benefit and risk.
Moderate	Data derived from a single RCT or multiple nonrandomized studies.	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
Low	Small studies, retrospective observational studies, registries.	Any estimate of effect is uncertain.
Recommendations grade		**Wording associated with the grade of recommendation**
Strong		"must", "should", or "INASL recommends"
Weak		"can", "may", or "INASL suggests"
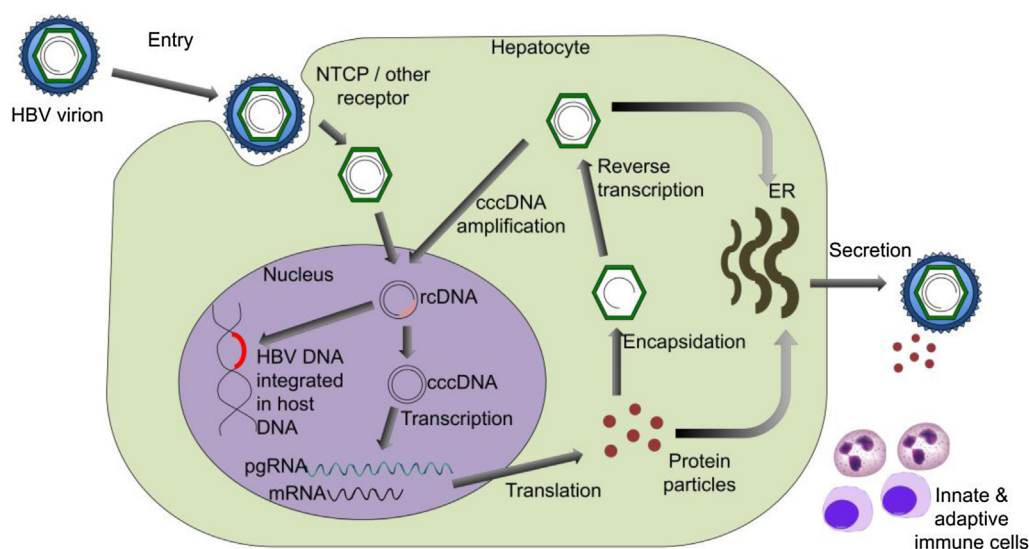
Figure 1 Life cycle of hepatitis B virus.

Impairment in HBV-specific T cell function leads to chronic HBV infection. HBV persistence is associated with virus-specific as well as global T cell dysfunction mediated by multiple regulatory mechanisms promoted by viral proteins in individuals with genetic susceptibility. HBV viral proteins down regulate pattern recognition by cells, bring about changes in Natural Killer cell receptors and lead to CD4 and CD8 T cell exhaustion.[15] Only hepatocyte death can lead to cccDNA clearance.

Natural History of HBV Infection

Clinical outcome in HBV infection depends on age of acquiring the infection. Perinatal transmission leads to almost 95% carrier rates, whereas when adults are exposed to HBV infection, only 2–5% of them develop Chronic Hepatitis B (CHB). The natural history of chronic HBV infection has been divided into distinct phases, as initially described by Chen.[16] These phases are as follows:

- Immune-tolerant phase
- Immune-active Hepatitis B Envelope Antigen (HBeAg)-positive phase
- Inactive carrier phase
- HBeAg-negative immune reactivation phase, and
- HBsAg-clearance phase.

These phases are of variable duration, may or may not be sequential, and not every person infected with HBV will pass through all phases.[17] These phases take into account the presence of HBeAg, HBV DNA levels, Alanine Aminotransferase (ALT) values and presence or absence of liver inflammation. However, a single determination of HBV replication markers and disease activity markers does not allow an accurate classification to one of these phases. Serial monitoring of HBeAg, HBV DNA and ALT levels is required in most instances to establish the phase of infection; despite which, some subjects fall into an indeterminate grey area and management needs to be individualized.[1,8] Recently EASL has suggested a change in nomenclature of these phases as follows: HBeAg positive chronic infection, HBeAg positive chronic hepatitis, HBeAg negative chronic

HBV Infection

Table 2 Phases of Chronic Hepatitis B.

Phase	Old name	New name	HBeAg	Serum HBV DNA	ALT	Liver histology
Phase I	Immune-tolerant phase	HBeAg positive chronic infection	Positive	$>10^7$ IU/mL	Normal	Minimal inflammation and fibrosis
Phase II	Immune-active HBeAg-positive phase	HBeAg positive chronic hepatitis	Positive	10^4–10^7 IU/mL	Elevated	Moderate-to severe inflammation or fibrosis
Phase III	Inactive carrier phase	HBeAg negative chronic infection	Negative	<2000 IU/mL	Normal	Minimal necroinflammation but variable fibrosis
Phase IV	HBeAg-negative immune reactivation phase	HBeAg negative chronic hepatitis	Negative	>2000 IU/mL	Elevated	Moderate-to severe inflammation or fibrosis
Phase V	HBsAg-clearance phase (also known as occult HBV infection)	HBsAg negative chronic infection	Negative	Undetectable (HBV DNA can be detectable in liver)	Normal, usually	No inflammation, minimal fibrosis. HBV DNA (cccDNA) can be detected frequently in the liver

infection, HBeAg negative chronic hepatitis, and HBsAg negative chronic infection, respectively.[3] Since, the new nomenclature is easy to understand and simpler to use in dichotomizing infected individuals into those with infection (no liver inflammation or damage) and those with hepatitis (with liver inflammation and/ or damage) it should be used widely. However, it may still not eliminate all grey areas as it continues to depend on ALT, which is an imperfect marker of liver injury. INASL has endorsed this new nomenclature for use in India.[1] A summary of features of all the five phases along with the new nomenclature is given in Table 2.

Acute Exacerbations in Natural History of HBV: Flares and Reactivation

The clinical presentation of chronic HBV infection depends on a dynamic state of interactions between the virus, host immunity and hepatocytes.[18] During the natural course of chronic HBV infection the relatively stable course is often interrupted by phases of increased necroinflammation: also called as 'flare'.[19] Various definitions of flare have been proposed, however, most experts accept that an abrupt elevation of serum ALT to >5 ULN or a greater than threefold increase in ALT is a flare.[18,20] The flares usually occur during the HBeAg positive chronic hepatitis (immune active phase)[20,21] and occur infrequently during the HBeAg-negative chronic hepatitis phase.[21,22] Any immune flare that occurs in immune active phase or occasionally in patients with HBeAg-negative CHB phase may lead to viral clearance. This flare of HBV infection is usually preceded by viral replication.

HBV reactivation is one of the causes of HBV flare. HBV reactivation is diagnosed when a patient with serologic evidence of HBV develops any one of these[23]:
- A detectable HBV DNA level when they previously had undetectable HBV DNA.
- A rise in HBV DNA of more than 2 $\log_{10}$ times in patients who had HBV DNA present at baseline. In some studies, HBV

reactivation is defined as more than one $\log_{10}$ times the baseline HBV DNA.
- Reverse seroconversion (when a patient previously HBsAg-negative/anti-HBc-positive becomes HBsAg-positive).

Pathogenesis of Flare Due to HBV Reactivation

A close interaction between the HBV, hepatocyte and host immunity (both innate and adaptive) decides the fate of HBV. Since, HBV is non-cytopathic virus, the major contribution to hepatocyte injury is due to activation of immune response against the hepatocytes.[21] Rise in serum HBeAg, HBV DNA and intracellular viral proteins precede the hepatocyte injury leading to clinical flare by several weeks.[24,25] Subsequent increase in anti-HBe production and HBeAg/anti-HBe immune complex formation signifies the role of the immune response in initiating the hepatitis flare.[26]

Immunohistologic studies during the hepatitis flares have shown strong membranous expression of Human Leukocyte Antigen Class I, increased CD8+ T cells in the mononuclear cell infiltrates, and cytoplasmic or membranous/submembranous HBcAg expression.[27] There is rise in HBcAg/HBeAg-specific T cell proliferation before and during the hepatitis flares; an increased production of interferon gamma, Th1 phenotypic cytokine IL-2, IFN-α and IL-8 during the flare.[28,29] The Treg cells decline during the flare, implicating exaggerated T cell mediated immune response[30]. This leads to immune mediated cytolysis of hepatocytes expressing HBV antigens and its downstream apoptotic mechanisms. A higher ALT level corresponds to more vigorous immune response against HBV. It is still not clear, however, what triggers the initiation of the immune cascade.[18]

Clinical Outcomes of Reactivation

The clinical spectrum of reactivation varies from totally asymptomatic to severe flares causing hepatic decompensation (jaundice and coagulopathy) or even leading to liver

failure. It can mimic overt acute hepatitis in 30% of patients. Incidence of hepatic decompensation depends on baseline liver status: decompensation occurs in 13.9% patients with cirrhosis and in 2–3% without cirrhosis, respectively.

Most of the HBV flares which are not complicated with decompensation have decreasing ALT to pre-flare levels within one month.[31] In HBeAg positive patients more than 80% flares subside within 3 months. On the other hand 30% of the flares in HBeAg-negative patients are followed by persistently abnormal ALT.[22]

HBeAg Seroconversion or DNA Suppression Following a Flare

A flare of HBV not only increases the risk of decompensation and liver related morbidity but also provides an opportunity to host to clear the virus. Flare can lead to HBeAg seroconversion and sustained DNA suppression ushering significantly decreased burden of the disease. However, not all patients who experience the flare achieve virus suppression. Baseline ALT level, bridging hepatic necrosis, Alphafetoprotein (AFP) levels, and genotype are some of the determinants for achieving viral suppression. A large Chinese study showed that patients with ALT > 5 × ULN at entry carried a 46% chance of HBeAg seroconversion within three months.[32] In another study patients with ALT > 5 × ULN at entry had a spontaneous HBeAg seroclearance rate of >50%, and a rate of >60% during 12 to 18-month follow-up. In contrast, patients with ALT < 5 × ULN at entry had <5% and <10% spontaneous clearance rates, respectively, at the corresponding time points.[33] In addition, of all the patients who had bridging hepatic necrosis on biopsy, 67% had HBeAg seroconversion by end of 12 months as compared to only 16% without bridging necrosis.[31] Level of AFP correlates with bridging hepatic necrosis and can also independently predict the HBeAg seroconversion.[33] Genotype B infected patients mount increased Th 1 mediated response and better seroconversion than genotype C which may need more robust immune system for removal of virus.[34,35] The killing of infected hepatocytes which are the home of cccDNA and further diluting it by subsequent regeneration leads to enhanced elimination or suppression of HBV during flare.[36] T cell mediated cytolysis, and cytokine-related suppression of HBV gene expression and replication lead to seroconversion. Host immune response is the chief determinant of outcome (effective vs ineffective clearance). About two-third of spontaneous HBeAg seroconversions are preceded by HBV flares in the preceding three months.[37,38] However, only a few HBV flares are followed by spontaneous HBeAg and/or HBV DNA seroclearance within 3 months.[33]

The pattern of HBV DNA and ALT dynamics is not only predictive of risk of liver failure but also guide to initiating treatment. Jeng et al. in their study showed that HBV DNA > 3 × 10^8 IU/mL along with increasing ALT during flare was predictive of subsequent hepatic decompensation, with a sensitivity and a specificity both of 86% and a negative predictive value of 99%.[39] These patients have ineffective immune clearance perhaps secondary to inadequate Th1 repsonse.[34] Such patients as well as cirrhotic patients with hepatitis flares require immediate anti-HBV therapy.[18] In contrast, patients whose serum HBV DNA starts to decrease before the ALT peak may have effective immune clearance, which may lead to HBV DNA/HBeAg seroclearance and disease remission.[40] It is thus reasonable to observe non-cirrhotic patients with hepatitis B flares for 3–6 months to know whether antiviral therapy is indeed required.[41] In another study from India, Tenofovir was able to significantly reduce HBV-DNA levels, improve CTP and MELD scores, and reduce mortality in patients with severe spontaneous reactivation of CHB presenting as Acute-on-Chronic Liver Failure (ACLF). The reduction in HBV-DNA levels at 2 weeks was a good predictor of survival.[42]

Usually multiple episodes of hepatitis flares lead to spontaneous HBeAg seroconversion or HBV DNA suppression with sustained remission. Patients who fail to clear HBeAg may continue to have normal ALT for a variable duration. This cycle can continue until HBV is suppressed to an inactive level i.e. HBeAg-negative, ALT normal and HBV DNA < 2000 IU/mL.

Reactivation Due to Immunosuppressive Therapy

When a patient with chronic HBV infection or hepatitis is subjected to immunosuppressive drugs or situations, HBV replication levels rapidly spurt into 'viral reactivation'. This is usually due to a decline in specific T cell control over the HBV replication, but may also be the result of direct stimulation of HBV replication. HBV reactivation is associated with a rise or appearance of HBsAg and HBV DNA.[3] Symptoms may be minimal at this stage. When immunosuppressive drugs are withdrawn, immune reconstitution takes place and cytotoxic T cells become active again. It may happen 7–10 days after a pulse of chemotherapy and may lead to immune elimination of infected hepatocytes and consequent necro-inflammation in liver.[43] Clinically it becomes evident as a rapid rise in ALT levels with or without development of typical acute hepatitis (flare). Rapid immune mediated destruction of a large mass of infected hepatocytes may cause acute liver failure. In some cases liver damage may resolve due to recovery of the immune system with or without use of antiviral drugs. Sometimes, the hepatitic illness may continue as in HBeAg negative CHB shown in phase 3 above.

Factors that determine severity of HBV reactivation include:

Table 3 Grading System for HBV Reactivation Due to Immunosuppressive Therapy.[47]

irological		Hepatic		Immunosuppression	
V_1	HBV DNA increase by >1 log IU/mL (or from undetectable to detectable)	H_0	No hepatitis: ALT remains <2 ULN, no change in bilirubin or INR	I_0	No consequence
V_2	Reverse seroconversion: reappearance of HBsAg with or without associated rise in HBV DNA	H_1	Hepatitis: ALT 2–10 × ULN with no associated change in bilirubin or INR	I_1	No interruption but increased frequency of HBV DNA and ALT monitoring
		H_2	Severe hepatitis: ALT > 10 × ULN and/or elevation of bilirubin (>2 ULN) or INR (>1.3)	I_2	Interruption of immunosuppressive therapy with re-initiation of same drug after hepatitis flare resolved
		H_3	Fulminant hepatitis: Same as H_2 along with development of encephalopathy or ascites	I_3	Interruption of immunosuppressive regimen with re-initiation of 2nd line, suboptimal, therapy
		H_4	Death: due to liver failure	I_4	Discontinuation of immunosuppression

(a) Host related factors: HBV reactivation is likely to be more severe in young males with pre-existing raised ALT;
(b) Viral factors: More severe with high HBV DNA, HBsAg and HBeAg levels[44] and in those with pre-core or core promotor mutants[45]; and
(c) Factors related to immunosuppressive agents: its potency, dose and duration (particularly severe after rituximab, anthracycline drugs and after stem cell transplantation).[46]

By combination of various factors, a system of classification has been proposed for HBV reactivation[47] (Table 3). This classification can be useful in categorizing patients for research in this area.

In all HBsAg positive patients, with raised ALT levels or bilirubin, superimposed injury to hepatocytes due other causes like Hepatitis A Virus (HAV), Hepatitis E Virus (HEV), Hepatitis D Virus (HDV), hepatotoxic drugs and autoimmune hepatitis should be ruled out. It is very important to distinguish the acute HBV related hepatitis vis-a-vis acute exacerbation of CHB (flare). In case of HBV flare (ALT > 5 × ULN) the condition may deteriorate to severe hepatitis or hepatic decompensation. It is imperative to know whether reactivation is spontaneous or secondary to precipitating event. All these patients should be monitored closely (weekly or biweekly serum ALT, bilirubin, and prothrombin time measurements) to detect clinical deterioration or hepatic decompensation in time for immediate antiviral therapy for prevention or rescue.[41]

Consensus Statements

- *Definition of HBV flare:*
  - *Flare is defined as an abrupt elevation of serum ALT to >5 ULN or a greater than threefold increase in serum ALT.*

(Evidence level hi strength of recommendation - strong)
- *Definition of HBV reactivation:*
  - *HBV reactivation is diagnosed when a patient with serologic evidence of HBV develops any of the following:*
  - *A detectable HBV DNA level when they previously had undetectable HBV DNA.*
  - *A rise in HBV DNA of more than 2 $\log_{10}$ international units/mL in patients who had detectable HBV DNA at baseline.*
  - *Reverse seroconversion (when a patient previously HBsAg-negative/anti-HBc-positive becomes HBsAg-positive).*

(Evidence level high, strength of recommendation strong)

PREVENTION OF HBV REACTIVATION IN PATIENTS RECEIVING CANCER CHEMOTHERAPY

Magnitude of the Problem

In India prevalence rate of overt HBV infection (HBsAg positive) is 1–5%,[1,2,48] while the reported incidence of anti-HBc positivity among healthy blood donors ranges from 17% to 29% suggesting past exposure to HBV. The prevalence of HBV infection in patients suffering with cancer is higher as compared to general population. A study from Kashmir revealed HBsAg positivity rate of 8% in cancer patients. Generally, the prevalence is more in hematological malignancies cancers with highest in Non-Hodgkin's Lymphoma (NHL)[49]. The etiology for increased prevalence of infection could include immunosuppression due to underlying cancer with falling anti-HBs titers and subsequent reactivation of HBV DNA especially in patients who are anti-HBc positive.

HBV Infection
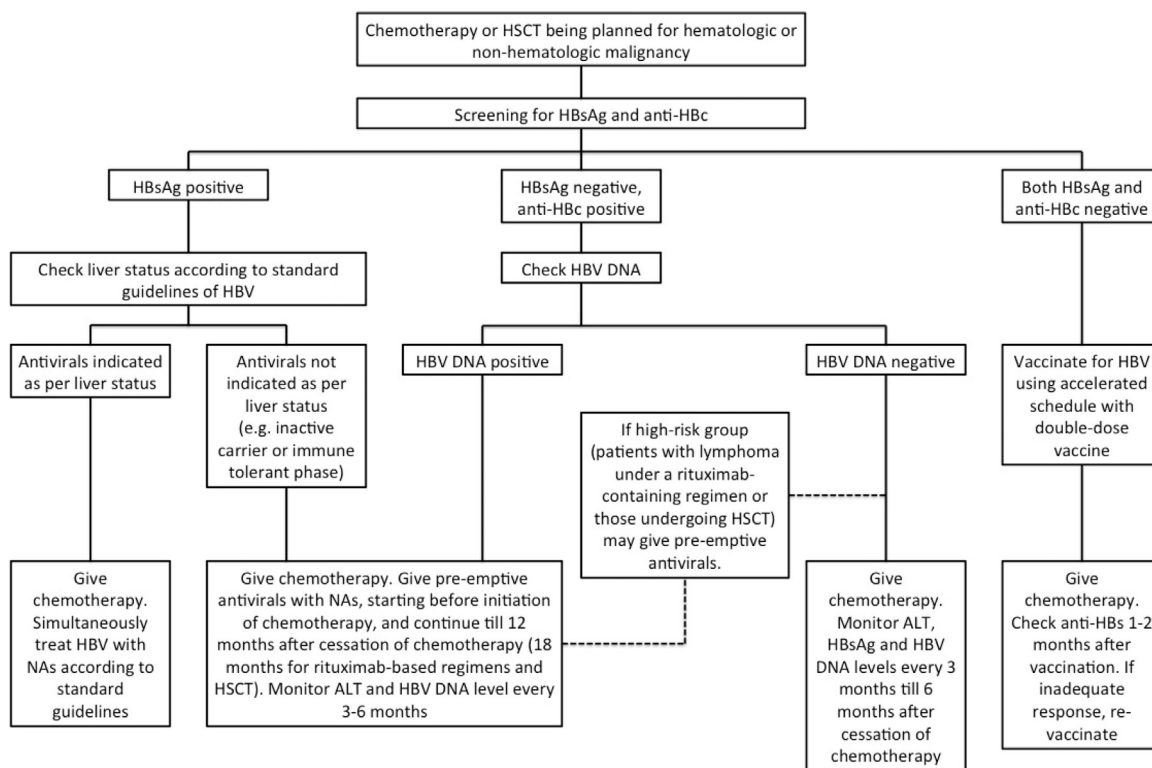
Figure 2 Algorithm for screening and prevention of hepatitis B virus (HBV) reactivation in patients being planned for chemotherapy of HSCT for hematologic or non-hematologic malignancy.

There is high rate of HBV reactivation in HBV-positive patients receiving cancer chemotherapy. Impaired host immunity due to chemotherapy increases the risk of HBV reactivation, however, its exact incidence is unclear. The reactivation can be in the form of exacerbation of chronic HBV infection, or in the form of relapse of past HBV infection. In landmark study published by Anna Lok et al. in 1990s, she studied 100 patients with NHL undergoing Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) chemotherapy.[50] At baseline, 27 of them were found to be HBsAg positive, 48% of these had reactivation, just under a quarter of whom became jaundiced, and there was one episode of non-fatal liver failure and one death. In HBsAg positive breast cancer patients receiving standard chemotherapy, the rate of HBV associated hepatitis has been associated to be as high as 21%.[51]

The incidence of cancer in India is one million new cases each year[52]; more than two thirds present in advanced stages each year (750,000 per year). All put together, majority of these cases are candidates for receiving cancer chemotherapy at some point or the other in their life span and hence at risk for reactivation of HBV infection.

The diagnosis of HBV reactivation requires the exclusion of other conditions such as chemotherapy Drug induced Liver Injury (DILI), liver metastases, and other types of viral hepatitis. Many patients with HBV reactivation are asymptomatic, but the clinical course varies widely from jaundice to decompensation or even death.[1,50,51,53,54]

The algorithm for the work up and treatment of these patients is summarized in Figure 2.

Non-Hematological Malignancies
Pre-chemotherapy Evaluation

It is recommended to screen for HBsAg and anti-HBc prior to initiation of immunosuppressive treatment or chemotherapy.[55] All patients found to be positive for HBsAg and candidates for chemotherapy should be referred to a specialist for further assessment and diagnosis of the phase of HBV infection, liver status (fibrosis or cirrhosis assessment), and to determine need for antivirals. If HBsAg is negative but anti-HBc is positive, serum HBV DNA should be tested. Patients without evidence of HBV infection should be vaccinated. Higher doses or reinforced vaccine may be required to achieve anti-HBs response in immunocompromised patients.[1,8]

When HBsAg is Positive

All these patients would require antiviral therapy either as a treatment or as prophylaxis. If the evaluation suggests that the patient needs antivirals for his liver status (i.e. chronic hepatitis or cirrhosis) he should be treated with

Entecavir (ETV), Tenofovir Disoproxil Fumarate (TDF) or Tenofovir Alafenamide (TAF), similarly to the immuno-competent patients, as per the standard guidelines, along with chemotherapy. If the evaluation suggests that he does not need antivirals for his liver status (i.e. inactive carrier or immune tolerant phase), he should receive pre-emptive antivirals with ETV, TDF, TAF along with chemotherapy. Prophylaxis should continue for at least 12 months after cessation of the chemotherapy and discontinued only if the underlying disease is under remission. Liver function tests and HBV DNA should be tested every 3–6 months during prophylaxis and for at least 12 months after Nucleos(t)ide Analog (NA) withdrawal as a large proportion of HBV reactivations develops after NA discontinuation.[1,8,56,57]

When HBsAg is Negative But Anti-HBc is Positive

When HBsAg is found negative but anti-HBc is positive, these patients should be tested for HBV DNA by RT PCR. If the HBV DNA is detectable, these patients should receive pre-emptive antivirals with ETV, TDF or TAF similar to HBsAg positive patients.

When Isolated Anti-HBc is Positive

The risk of HBV reactivation in this group varies widely according to the virological profile, underlying disease and the type and duration of immunosuppressive regimen.[8] Seroreversion (or reverse seroconversion) is the redevelopment hepatitis B surface antigenemia, HBV DNA viremia with or without hepatitis as a result of reactivation of "occult" infection triggered by chemotherapy or immunosuppression. HBsAg-negative, anti-HBc positive patients with undetectable serum HBV DNA, who receive chemotherapy and/or immunosuppression regardless of anti-HBs status, should be followed carefully by means of HBsAg, ALT and HBV DNA testing. The frequency of monitoring can range from 1 to 3 months, depending on the type of immunosuppressive therapy and co-morbidities. The main virological event in these anti-HBc positive patients is HBsAg reappearance (seroreversion), constantly associated with hepatitis flare. These patients need pre-emptive therapy, and not prophylaxis.[1,8,56,58] Pre-emptive therapy is based upon monitoring HBsAg and/or HBV DNA every 1–3 months during and after immunosuppression, and starting ETV, TDF or TAF treatment in case of detectable HBV DNA or HBsAg seroreversion. As HBsAg seroreversion can lead to a severe, even fatal, acute hepatitis, NA should be started immediately on detection of positive HBsAg or HBV DNA.[8,41,59–61]

Hematological Malignancies

Most current HBV treatment guidelines club together various conditions requiring immunosuppressants. Hematological malignancies on the other hand represent a bigger challenge as regards to HBV reactivation. Besides being an immune-suppressed state *per se*, complicated and often repeated chemotherapeutic regimen, frequent use of monoclonal antibodies targeting immune cells and Hematopoietic Stem Cell Transplant (HSCT); make it difficult to ascertain with any degree of certainty the risk of HBV reactivation and also the length of immune suppression. This increases the complexity in managing HBV infection in patients with hematological malignancies.

A recent systematic review summarized evidence from 42 published studies (randomized trials: 7, prospective cohort studies: 9, retrospective studies: 24 and combined retrospective-prospective studies: 2) on managing HBV in the setting of hematological malignancy and HSCT.[62] In patients with lymphoma not receiving prophylaxis, HBV reactivation varies from 24% to 85% in HBsAg-positive patients and 4% to 42% in patients with resolved HBV infection. The risk seems to be higher with the use of Rituximab (and any other anti-CD20 antibody). Limited data suggests lower reactivation rates in patients with non-lymphoma hematological malignancy (5–28% in HBsAg-positive and 2–20% in resolved HBV infection).[62]

Pre-Therapy Evaluation

Although effectiveness of screening and specific protocol therein, has not been tested in any prospective/randomized study; two recent randomized trials on HBsAg-positive lymphoma patients, have shown significant decrease risk of HBV reactivation or hepatitis flares with use of Lamivudine (LAM) as prophylaxis.[63,64] The data, although limited and indirect, argues for routine screening (with HBsAg and anti-HBc antibody) in all patients with hematological malignancy. As viral reactivation precedes hepatitis flares, most studies employ HBV DNA (highly sensitive quantitative assay) as a monitoring tool.[55] In patients with resolved infection, reverse sero-conversion can be monitored with HBsAg testing. As the timing of flare is variable and unpredictable, in most studies monitoring varies from 1 to 3 month to a period varying from 1 to 5 years after the chemotherapy.[62]

When HBsAg is Positive

Recent two small randomized studies (one with 15 patients in each arm and the other with 25 patients in each arm) in HBsAg-positive lymphoma patients receiving non-Rituximab based chemotherapy regimens have shown clear benefit in using LAM as an early pre-emptive prophylaxis compared to deferred pre-emptive treatment on detection of virologic reactivation. There was decreased incidence of HBV reactivation (0 and 12% v/s 53% and 56% respectively) and hepatitis flares.[63,64] Multiple other retrospective studies have shown benefit of LAM prophylaxis in preventing HBV reactivation.[62] A recent randomized

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study compared the efficacy of prophylactic use of ETV versus LAM in HBsAg-positive lymphoma patients on Rituximab based chemotherapy.[65] There was a 23% decrease in HBV reactivation (7% versus 30%) with ETV use. This translated into significantly lesser hepatitis flares and chemotherapy disruptions. In a small and heterogenous prospective cohort study with historical controls, TDF was found superior to LAM as a prophylaxis in this setting[62].

Optimal duration of prophylaxis after cessation of chemotherapy is unclear. Studies have continued for 2–18 months post chemotherapy. Late reactivation (after stopping prophylaxis) is not an uncommon occurrence and monitoring needs to be continued even after cessation of prophylaxis.[62]

When Isolated Anti-HBc is Positive

In a five-year prospective study from Italy, of the 17 HBsAg-negative but anti-HBc-positive with hematological malignancies receiving intravenous cytotoxic chemotherapy, three (18%) had reactivation with seroreversion.[66] Multiple prospective studies with Rituximab receiving lymphoma patients have also shown the HBV reactivation rate varying from 8% to 30% with a high risk of chemotherapy disruption (5–47%).[62,67,68] The estimate of HBV reactivation with other hematological malignancies is based on small retrospective studies and varies from 5% to 20%.[62] Two recent randomized trials compared prophylaxis to pre-emptive strategy in lymphoma patients with resolved HBV infection, receiving Rituximab based chemotherapy.[69,70] Prophylactic ETV and TDF use decreased the incidence of HBV reactivation (2% and 0% versus 18% and 11%, respectively). The duration of therapy varied and was 3 and 12 months post cessation of chemotherapy respectively.

Prophylaxis in Patients Receiving HSCT

There are no prospective or randomized studies to guide our decision in this area. Few retrospective studies have documented a HBV reactivation rate varying from 45% to 50% in patients with allogeneic or autologous HSCT.[71–73] The rate of reverse seroconversion in patients with resolved infection varied from 10% to 25%.[74] Retrospective studies have shown decrease in HBV reactivation with use of LAM and ETV as prophylaxis, especially in HBsAg-positive patients.[73,75]

In allogeneic HSCT, donor Hepatitis B status may also play a role in HBV reactivation. There are high chances of recipient HBV reactivation if donor is HBsAg-positive. It may be prudent to avoid such donors if possible or prophylactic antivirals (with or without Hepatitis B Immune Globulin (HBIG)) may have to be used.[72,76] Although the role of donor vaccination in resolved HBV infected recipients is still unclear,[77] this can be considered.

Pediatric Aspects of HBV Reactivation During Management of Childhood Malignancies

Although the likelihood of reactivation is theoretically possible in children, there are no guidelines available in world literature or by the North American (NASPGHAN) or European (ESPGHAN) Pediatric Gastroenterology, Hepatology and Nutrition Societies in this regard. LAM, ETV and TDF have been approved for use in children. LAM is approved in children >2 years at a dose of 3 mg/kg (maximum dose of 100 mg); ETV in children >2 years of age in the dose of 0.15 mg up to 10 kg and maximum up to 0.5 mg; and TDF in children >12 years of age, weighing >35 kg with a maximum dose of 300 mg.

Extrapolating from the adult population, HBsAg and anti HBc testing needs to be done in all children prior to starting chemotherapy. Antiviral drugs need to be started in all who are HBsAg positive before initiating chemotherapy and continued for 12 months after stopping chemotherapy.

High risk group would include HSCT recipients, patients needing high dose steroids in doses of more than 20 mg for more than 4 weeks, children needing B cell depleting agents like Rituximab or Anthracycline derivatives (Epirubicin, Doxorubicin).[78] This group may be started on antivirals even if they are isolated anti-HBc-positive without HBsAg or HBV DNA positivity and treatment continued for 18 months after stopping drugs like rituximab. HSCT recipients should continue treatment lifelong. Interferon based treatment is not recommended in this group of patients.

More than 80% of childhood cancer survivors are negative for serological markers of HBV.[79] It is recommended that they need to be tested for anti-HBs antibody and if unprotected, they should be vaccinated

Consensus Statements

- *All patients (both adult and pediatric) with hematologic or non-hematologic malignancies who are candidates for chemotherapy, immunosuppressive therapy or HSCT need to be screened with HBsAg and anti-HBc.*
  (Evidence level high, strength of recommendation strong)
- *If HBsAg is found positive these patients should be referred to a specialist for further assessment and diagnosis of the phase of HBV infection, liver status, and any need for antivirals.*
  (Evidence level high, strength of recommendation strong)
- *If HBsAg is found negative but anti-HBc is positive, serum HBV DNA should be tested.*
  (Evidence level high, strength of recommendation strong)
- *All those who are found negative for both HBsAg and anti-HBc, vaccination should be initiated. Higher doses or reinforced vaccine may be required to achieve anti-HBs response in immunocompromised patients.*

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(Evidence level high, strength of recommendation strong)

- *Pre-emptive antiviral prophylaxis with ETV, TDF or TAF is recommended for patients when HBsAg or HBV DNA is positive.*
  (Evidence level high, strength of recommendation strong)
- *Treatment should be continued for at least 12 months after discontinuation of chemotherapy or immunosuppressive therapy (18 months for rituximab-based regimens and HSCT).*
  (Evidence level moderate, strength of recommendation strong)
- *Patients who have only isolated anti-HBc positivity should be monitored with HBsAg, ALT and HBV DNA testing every 3 months during therapy and up to 6 months after.*
  - *Pre-emptive antiviral therapy with ETV, TDF or TAF should be started immediately on detection of HBsAg or HBV DNA positivity.*
  - *Pre-emptive antiviral therapy in patients with isolated anti-HBc-positive (with HBsAg and HBV DNA negative) can be initiated in high-risk groups such as patients with lymphoma under a rituximab-containing regimen or those undergoing HSCT.*
  (Evidence level moderate, strength of recommendation strong)
- *In children following drugs should be used for pre-emptive prophylaxis or therapy*
  - *ETV for children >2 years of age*
  - *ETV or TDF for children >12 years of age.*
  (Evidence level moderate, strength of recommendation strong)

HBV PATIENTS RECEIVING BIOLOGICALS FOR NON-MALIGNANT DISEASES

Biological agents are used for a variety of rheumatological, dermatologic and gastrointestinal diseases. When HBV-infected individuals are exposed to biologicals for these diseases the risk and consequences of HBV reactivation is quite significant. The risk of HBV reactivation is most commonly seen in HBsAg positive subjects, but may also occur in patients with occult HBV infection. In overt carriers with high viral load, flare due to reactivation may occur *during* the biological treatment. However in most cases the reactivation usually occurs following the cessation of biological treatment.[80] Biological drugs differ in their ability to cause reactivation of HBV.[55] Rituximab,[81,82] and monoclonal anti-TNF antibodies[83,84] carry the highest risk of reactivation (>10%) followed by etanercept,[85] abatacept,[86] and kinase inhibitors which carry moderate risk (1–10%).

Most of the data on this aspect has come from rheumatological studies where biologic drugs have been used extensively. The clinical spectrum of HBV reactivation varies widely from asymptomatic biochemical, virological abnormalities to fatal acute liver failure. The early phase of reactivation can only be diagnosed by prospectively investigating and can be treated by providing prophylactic or pre-emptive antiviral treatment. The occurrence of jaundice in a patient who is a HBV carrier receiving a combination of immunosuppressant drugs is a diagnostic challenge as it could either be due to drug induced toxicity or as a manifestation of the reactivation. In this situation significant HBV DNA elevation over the baseline value would suggest HBV reactivation as the cause of the jaundice and would argue against drug induced hepatotoxicity.

In view of the risk of reactivation of HBV, it is mandatory to test for HBV markers prior to commencement of therapy with these drugs. Current evidence suggest that only two serological markers are mandatory prior to commencement of biologic therapy: HBsAg and anti-HBc. The algorithm for the work up and treatment is summarized in Figure 3.

Biologicals for Inflammatory Bowel Disease

The two most common anti-TNF drugs used for IBD, available in India currently, are infliximab and adalimumab. Current guidelines from the European Crohn's and Colitis Organisation (ECCO) recommend testing for HBV before starting immunosuppressive treatment for IBD.[87] Assessment of HBsAg and anti-HBc are recommended as initial screening tests. In HBsAg-positive patients the evaluation should follow the standard guidelines for HBV management to define the HBV profile (chronic HBV infection, chronic HBV hepatitis or cirrhosis), since this status dictates the need for HBV treatment, prophylaxis, or simple monitoring. In patients who merit HBV treatment on the basis of their HBV status, the safety and efficacy of NAs in IBD patients have been confirmed in case series and study cohorts.[88] Treatment duration in these patients is dictated by the need of treating HBV chronic hepatitis per se, independently from immunosuppressive therapy for IBD.[88] In HBV patients with IBD, administration of IFN is not recommended due to the potential risk of IBD exacerbations.[87]

In HBsAg-positive inactive carriers the risk of HBV reactivation in IBD patients undergoing immunosuppressive therapy ranges from 20% to more than 30% and requires prophylaxis of HBV reactivation by NAs. Risk of HBV reactivation depends on the type of biologic agent administered: patients on anti-TNF drugs and integrin inhibitors are considered at moderate risk, so prophylaxis is mandatory.[88] Prophylaxis should be carried on for the entire duration of immunosuppressive treatment and prolonged after the discontinuation of biologics due to the fact that the risk of HBV reactivation is higher when immune reconstitution occurs. ETV or TDF/TAF are the recommended drugs for prophylaxis of HBV reactivation.[88]

HBsAg-negative, anti-HBc-positive patients efficiently resolved HBV infection and do not display serological viral replication. However, HBV ccDNA can be found in
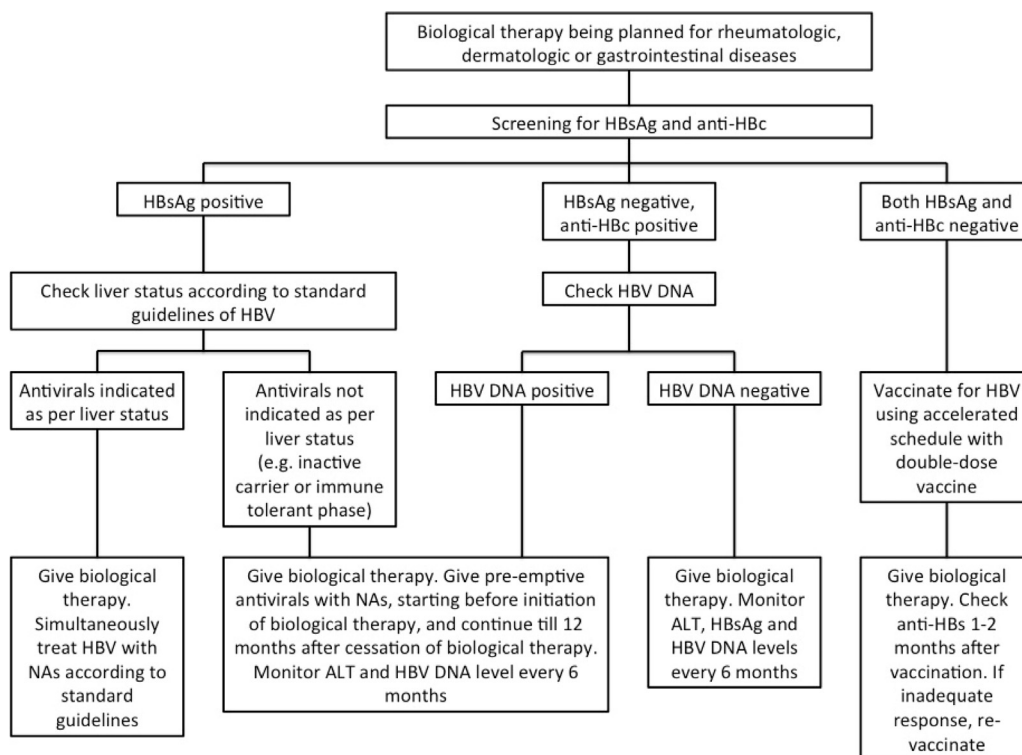
Figure 3 Algorithm for screening and prevention of hepatitis B virus (HBV) reactivation in patients being planned for biological therapy.

hepatocytes and a profound immunosuppression can result in restarting viral replication and HBsAg serum reappearance, the so-called seroreversion.[89] In IBD patients, as well as in rheumatologic diseases, the level of immunosuppression is lower and only isolated cases of seroreversion are described, so that guidelines recommend only periodical (every 3–6 months) monitoring of HBsAg and HBV-DNA, to early detect potential seroreversion and start HBV treatment promptly. The suggested NAs to treat seroreversion are again third-generation NAs ETV and TDF/TAF, due to the potent antiviral activity and fast virological suppression.[88]

Anti-HBV vaccination is recommended in all IBD patients with negative HBV serology: in patients receiving concurrent treatment with immunosuppressants, the standard schedule for HBV vaccination has been shown ineffective in conferring adequate seroprotection.[90] An accelerated schedule with double-dose recombinant HBsAg (40 mcg at 0, 1 and 2 months) has been advocated as the best vaccination strategy for IBD patients. In the REPENTINA-3 multicenter study, administration of accelerated double-dose recombinant vaccine provided seroprotection (anti-HBs titer 10–100 mIU/mL) in 43% IBD patients and effective vaccination (anti-HBs > 100 mIU/mL) in 27%.[91] Another study in 241 IBD patients showed higher efficacy rates, respectively,

59% for seroprotection and 42% for vaccination.[92] Serological response to vaccination should be checked after 1 or 2 months, and revaccination is recommended in patients failing to achieve adequate response after a first vaccine course. As seroprotection loss can occur long-term, regular monitoring of anti-HBs titles should be performed preferably every 2 years, and a unique booster dose is recommended to restore anti-HBs title > 100 mIU/mL, especially in patients undergoing anti-TNF treatment.[87]

Biologicals for Rheumatological and Dermatological Diseases

There is scant information on the prevalence of HBV infection in patients with rheumatologic diseases. Watanabe et al. from Japan reported that 1.1% of patients with Rheumatoid Arthritis (RA) and 0.3% of patients with Systemic Lupus Erythematosus (SLE) were positive for HBsAg.[93] They also found that occult HBV infection was much more common as revealed by anti-HBc positivity of 25.2% in RA and 13.7% in SLE. This occult infection can get reactivated when biological therapies are administered.[94]

Similar data from India is scarce. The prevalence of HBV infection in general population in India has been

estimated to be in the range of 1–4%.[1,2,95] HBV screening is routinely done in rheumatology practice whenever treatment with biological drugs is considered. Traditionally, HBsAg positivity constituted a contraindication to biological therapy.[96] A preliminary survey among rheumatologists in India shows that occult HBV infection (HBsAg negative, anti-HBc positive) is not being screened routinely. There is no data available on reactivation of occult HBV infection following biological therapy in patients with rheumatologic diseases in India.

In series from Spain[97] HBV reactivation was reported in 39% HBsAg positive carriers. In the same series the HBV reactivation rate in anti-HBc positive patients was 5%. While in a series from South Korea,[85] the incidence of HBV reactivation in anti-HBc positive patients 1.7%. Differences in the prevalence of HBV infection, viral genotype, or interval of HBV DNA monitoring could account for the differences in the incidence of reactivation among these reports. In a recent multi-center, observational, prospective study from Japan the incidence of HBV reactivation in patients with rheumatologic diseases with resolved HBV infection was 1.93/100 person-years, and the incidence of quantitative HBV DNA positivity was 0.55/100 person-years. None evoked clinical hepatitis in reactivated patients.[94] Mo et al.[98] have shown that in real world experience, 71% of patients with RA with HBV carrier state (positive HBsAg, normal ALT ≥ 6 months and normal total bilirubin) who discontinued antiviral prophylaxis, developed HBV reactivation 3–21 months after discontinuation; thus underscoring the need for constant monitoring for patient compliance. However in this Chinese study biologics have been used in very small number of patients.[98].

As compared with rheumatologic diseases, there is paucity of published literature about HBV reactivation in dermatological conditions where biologics have been used. Recently a number of anti-TNF-α agents have been widely used in the treatment of psoriasis. In a systematic search of all published reports of psoriatic patients, Cannizzaro et al. identified ten reports describing HBV reactivation during adalimumab, etanercept, golimumab or infliximab therapy.[99] The authors concluded that in psoriasis, the overall assessed risk of HBV reactivation is lower. In a meta-analysis of pooled dermatologic and rheumatic patients Cantini et al, have found that the incidence risk of HBV reactivation was low and ranged from 4.2% to 6.8%, with higher HBV reactivation recurrences in CHB carriers than in occult carriers[100].

The proposed guidelines for managing monitoring and managing HBV reactivation in patients with rheumatologic and dermatologic diseases receiving biologics are similar as proposed for inflammatory bowel diseases.[84,87,99,101] It is felt that there is a need to serologically monitor all patients being treated with biologics for

possible de novo HBV hepatitis and to promptly manage reactivation.

Consensus Statements

- *HBsAg and anti-HBc testing is recommended in all patients with rheumatologic, dermatologic or inflammatory bowel disease before receiving biologic therapy.*
  (Evidence level high, strength of recommendation strong)
- *Patients found positive for HBsAg, who are eligible to receive antivirals, should be treated with NAs (ETV, TDF, or TAF) as per standard guidelines, simultaneously while receiving biologic therapy.*
  (Evidence level high, strength of recommendation strong)
- *Patients found positive for HBsAg, but who are not eligible to receive antivirals for their liver status, should be started with pre-emptive antivirals with ETV, TDF or TAF before starting biologic therapy, and should be continued till 12 months after cessation of biologic therapy.*
  (Evidence level moderate, strength of recommendation strong)
- *Patients found to be HBsAg-negative but anti-HBc positive should be tested for HBV DNA.*
  - *Those found to have detectable HBV DNA should be treated with pre-emptive antivirals with ETV, TDF or TAF before starting biologic therapy, and should be continued till 12 months after cessation of biologic therapy.*
  - *Those found to have undetectable HBV DNA should be monitored for ALT, HBsAg and HBV DNA every 6 months till 12 months after cessation of biologic therapy. If HBsAg or HBV DNA becomes positive, they should be treated with pre-emptive antivirals with ETV, TDF or TAF till 12 months after cessation of biologic therapy.*
  (Evidence level moderate, strength of recommendation strong)
- *Patients found negative for all markers of HBV should be vaccinated for HBV by an accelerated schedule with double-dose recombinant vaccine.*
  - *Serological response to vaccination should be checked after 1 or 2 months of completion of vaccination, and revaccination is recommended in patients failing to achieve adequate response.*
  (Evidence level moderate, strength of recommendation strong)

MANAGEMENT OF HBV PATIENTS UNDERGOING SOLID ORGAN TRANSPLANTATION

Before the advent of effective antiviral agents for treatment of HBV infection, the presence of HBV infection was considered a contraindication for organ transplantation. HBsAg positivity was shown to be associated with an increased risk of renal allograft loss and death.[102] However, significant developments over the last two decades in the understanding and treatment of HBV infection led to a reappraisal of the guidelines for prophylaxis of HBV infection in solid organ transplant recipients with good clinical outcomes.[103]

Liver transplantation is one of the most common solid organ transplantation, being done in patients with HBV infection, as HBV itself is one of the causes for liver transplantation. Until the mid-1990s liver transplantation for end-stage liver disease due to HBV was associated with a substantially diminished graft survival because of the increased incidence of HBV reactivation and graft loss in recipients.[103] With the advent of antiviral agents such as NAs and HBIG, however, the risk of reactivation of hepatitis B and graft reinfection has been substantially reduced. Now with appropriate prophylactic therapy, liver transplantation in patients with CHB is associated with excellent long-term outcomes. However, the high cost associated with HBIG treatment still represents a major financial burden in developed countries, as well as in HBV endemic countries with limited financial resources. This has led to the consideration of prophylaxis without HBIG for selected patients undergoing liver transplantation.[103]

Management of HBV in Patients in Transplant Waiting List

HBV infected patients with decompensated cirrhosis have a poor outcome without treatment with an estimated 5-year survival rate of 14%.[104] The antiviral agents, especially NAs, are highly effective in suppressing the HBV replication in this population. The main purpose of antiviral therapy in this group of patients is to achieve clinical stabilization and to avoid liver transplantation if possible.[59,105] There is sufficient evidence today that antiviral therapy significantly modifies the natural history of decompensated cirrhosis, improves the liver function and the overall survival.[105–107] Approximately, 35% of patients treated with NAs can be delisted from liver transplantation list, and an improvement of CTP score ≥2 is observed in at least 40–50%. Also patients with early treatment initiation have better clinical outcome than those with delayed treatment.[107] High baseline CTP or MELD score are predictor of poor survival indicating advanced nature of disease.[106–109] In contrast, an improvement in MELD or CTP score early on-treatment is highly predictive of good transplant-free survival.[59,107,108] Undetectable HBV DNA levels can be achieved in >80% after one year of treatment, and are associated with a lower risk of HCC development.[106,107,110]

All patients with HBV-related decompensated cirrhosis should be treated with antiviral agents as early as possible with the aim of achieving complete viral suppression and clinical recompensation. It is to be noted that antiviral therapy should be started irrespective of HBV replication and should be continued lifelong. In those patients undergoing liver transplantation, the antiviral treatment needs to be continued post transplantation as well. Although several antiviral agents are available, NAs with high genetic barrier to resistance such as ETV, TAF or TDF

should be used.[59,111–115] Besides being highly effective in achieving viral suppression, all these agents have been found to be relatively safe in decompensated cirrhosis. There remains a concern of lactic acidosis in patients with decompensated cirrhosis during treatment with ETV and Tenofovir. This may be a class effects of NAs, and close monitoring for adverse event is recommended for patients with a MELD score of >22 and impaired renal function.[104,116] Doses of both ETV and TDF should be adjusted to renal function. Because of its favorable safety profile, TAF can be a good treatment option in patients with decompensated cirrhosis, especially in those with renal dysfunction. However, studies on safety and efficacy of TAF in decompensated cirrhosis are lacking.[8]

Pegylated Interferon Alpha (PegIFN-α) is contraindicated in patients with decompensated liver disease because of risk of worsening of liver disease and infectious complications.[8] Also, patients with decompensated liver disease have cytopenias (anaemia, low platelet, low Total Leucocyte Count (TLC)) that further contraindicates the use of PegIFN-α in these patients.

Consensus Statements

- *There is strong evidence that antiviral therapy significantly modifies the natural history of decompensated cirrhosis, improving liver function and increasing survival.*
  (Evidence level high, strength of recommendation strong)
- *Patients with decompensated cirrhosis should be immediately treated with a NA with high barrier to resistance (TDF, ETV, TAF), irrespective of the level of HBV replication, and should be continued lifelong, even for those undergoing liver transplantation.*
  (Evidence level high, strength of recommendation strong)
- *PegIFN-α is contraindicated in patients with decompensated cirrhosis.*
  (Evidence level high, strength of recommendation strong)

Management Protocol During and After Transplantation

Recurrence of HBV infection after liver transplant was associated with high mortality before the introduction of oral antivirals. Recurrence of HBV after liver transplant is defined as appearance of HBsAg with or without HBV DNA. This definition has been questioned, as it is only reappearance of circulating virion that predicts graft loss after transplant.

Oral antivirals that were started before liver transplantation (ETV, TDF, TAF), should be continued after transplant in all patients. A combination of high potency oral antivirals with high dose HBIG had been recommended based on various meta-analysis.[117–120] However, all these meta-analysis had mostly included studies where LAM
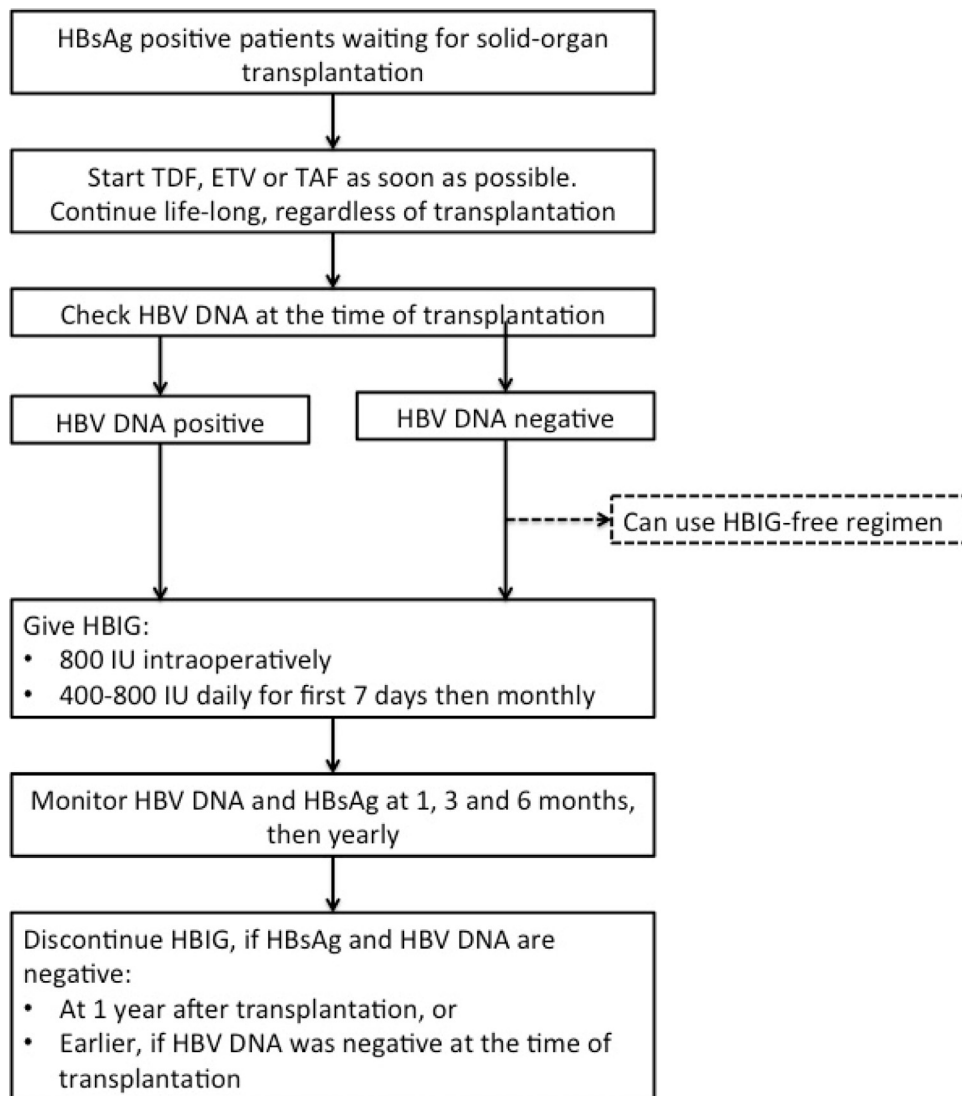
Figure 4 Algorithm for management of HBV patients undergoing solid organ transplantation.

and/or Adefovir (ADV) have been used. With the use of high potency antivirals like TDF/TAF and ETV, the need for HBIG in the immediate post-transplant period has been questioned.[8] There are many studies that have not used HBIG at all in the immediate post-transplant period.[121–123] All these studies have reported HBV recurrence rates of <10% that are comparable to HBIG regimens. With the available evidence, we would recommend that HBIG could be omitted in patients who are HBV DNA negative at the time of transplant. More data is required before we can recommend use of HBIG-free regimens in patients who are DNA positive at transplant.

HBIG withdrawal has been shown to be safe and does not increase recurrence of HBV infection[124–127]. HBIG withdrawal has been done as early as on first post-operative day after transplant. However, most centers would withdraw HBIG after 1 year provided the patients are HBsAg as well HBV DNA negative.

Thus, with the currently available evidence it is safe to recommend usage of low dose HBIG[128,129] (800 IU intraoperatively, followed by 400–800 IU daily for 7 days and then monthly) in patients who are HBV DNA positive at the time of transplant. Patients who are HBV DNA negative at transplant can be given only high potency oral antivirals and HBIG can be avoided.

Monitoring of HBV after transplant should be done with HBsAg and HBV DNA. Both tests should be performed at 1, 3 and 6 months after transplant and subsequently yearly. The algorithm for management of HBV patients undergoing solid organ transplantation is given in Figure 4.

Consensus Statements

- *Management protocol after transplantation:*
  - *Continue oral antivirals (TDF, ETV, TAF) in all patients.*

○ *Low dose HBIG should be given if HBV DNA is positive at the time of transplant:*
○ *800 IU intraoperative*
○ *400–800 IU intramuscularly (or 10,000 IU intravenously) daily for first 7 days and then monthly thereafter*
(Evidence level high, strength of recommendation strong)

- *HBIG discontinuation:*
  ○ *One year after transplant in patients who are HBV DNA and HBsAg negative.*
  (Evidence level high, strength of recommendation strong)

- ○ *Early discontinuation can be considered if HBV DNA and HBsAg are negative, and HBV DNA was negative at the time of transplantation.*
  (Evidence level low, strength of recommendation weak)

- *Status of HBIG-free regimen:*
  ○ *Can be used for patients with undetectable HBV DNA at the time of transplant.*
  (Evidence level low, strength of recommendation weak)

- ○ *More data is required before we can use HBIG-free regimen in patients who are HBV DNA positive at the time of transplant.*
  (Evidence level high, strength of recommendation strong)

- *HBV monitoring post-transplant:*
  ○ *HBV DNA and HBsAg should be done at 1, 3 and 6 months, then yearly.*
  (Evidence level moderate, strength of recommendation strong)

Organ Transplantation in Recipients Who are Isolated Anti-HBc Positive

Although reactivation of HBV replication has been reported in recipients who are HBsAg negative but anti-HBc positive pre-transplant, none of the recipients became HBsAg-positive or developed CHB after transplantation. Thus, prophylactic antiviral therapy is not warranted routinely after liver transplantation in HBsAg-negative, anti-HBc-positive recipients.[103,130] These patients should have monitoring of serum HBV DNA load, every 3 monthly in the first year and yearly thereafter. It is also reasonable to monitor ALT periodically in the post liver transplantation setting in those who are not receiving prophylactic therapy. Such patients should be considered for antiviral therapy with NAs as soon as serum HBV DNA becomes detectable, which should be continued lifelong. Furthermore, de novo HBV infection post liver transplantation is high (38.9% vs 4%; $P = 0.004$) if occult HBV infection is present in the recipient (defined as positive HBV DNA in liver tissue).[131]

Consensus Statements

- *HBsAg negative recipients who are positive for serum HBV DNA with or without total anti-HBc positivity should receive life-long prophylaxis with NAs.*
  (Evidence level high, strength of recommendation strong)

- *HBsAg negative recipients who are only total anti-HBc positive should have monitoring of serum HBV DNA load, every 3 monthly in the first year and yearly thereafter.*
  (Evidence level moderate, strength of recommendation strong)

Organ Transplantation From Donors Who are Isolated Anti-HBc Positive

The prevalence of HBV infection among donors is high in many regions of the world. In India the prevalence of total anti-HBc positivity varies from 16% to 20% in general population.[132,133] Variable rates of de novo HBV infection have been reported, depending on the serologic profile of the recipient and on the type of preventive therapy employed in the recipient post-transplantation. Some studies had shown protection against de novo HBV infection with the presence of anti-HBc antibodies (indicative of a previous HBV infection) and/or anti-HBs antibodies (indicative of previous vaccination or infection) among liver transplantation recipients.[134,135] Various preventive strategies, including revaccination, the use of antiviral drugs such as LAM, or the administration of human-specific HBIG, have been adopted by transplant centers, to prevent de novo HBV infection.[134–136] However consensus on the type of preventive strategies has not been well defined.

Different studies have used different criteria to define de novo HBV infection. Some studies have used appearance of HBsAg in a recipient who were previously HBsAg negative, while a few studies have used presence of HBV DNA either in serum or in the liver tissue for the diagnosis of occult de novo HBV infection.[120,136,137] Cholangitas et al.[120] in a systemic review found that in total, de novo HBV infection was observed in 19% of recipients at a median of 24 (5–54) months after liver transplantation. Post-transplant anti-HBV prophylaxis significantly decrease the probability of de novo HBV infection, which developed in 28% of recipients without, and 8% of recipients with post-transplant prophylaxis ($P < 0.001$). De novo HBV infection after liver transplantation with grafts from anti-HBc positive donors developed in 47.8% of HBV naive recipients (HBsAg negative with total-HBc negative) compared to 15.2% of recipients with serological markers of past HBV infection ($P < 0.001$). With anti-HBc positive liver grafts, the de novo HBV infection rate was 13% in recipients if HBsAg and anti-HBs are negative and only anti-HBc positive; while it was only 1.4% if recipient was anti-HBs positive. De novo HBV infection developed in 9.7% of patients in whom pre-transplant vaccination was given but had received no post-transplant prophylaxis.[120,137]

In a retrospective collaborative Italian multicenter study the incidence of de novo hepatitis was high among naïve liver recipients, while, despite an absence of prophylaxis, no HBV transmission was observed among heart, and kidney recipients independent of HBV profile. It was

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concluded that the risk of HBV transmission from anti-HBc positive donors is negligible for kidney and heart transplantation.[138] In a recent review of nine studies with 1385 HBsAg-negative kidney recipients from anti-HBc positive donors, new HBV serologic markers were observed in only 45 (3.2%) patients. Although this study did not explore the influence of recipient anti-HBs status and the use of prophylactic therapy, the rate of HBsAg acquisition was only 0.28% (4/1385) with no evidence of symptomatic hepatitis. Patient and graft outcomes were not worse among the patients with HBsAg acquisition.[139] In a post-hoc analysis of a limited-access dataset of the United Network for Organ Sharing database from 2000 to 2010, anti-HBc positive donor status did not significantly affect overall survival of thoracic transplant recipients.[140]

Consensus Statements

- *Persons with anti-Hbc can be considered for organ donors.*
  (Evidence level moderate, strength of recommendation strong)

- *Risk of de novo hepatitis is high in patient with liver transplant and low in lung, heart and renal transplantation.*
  (Evidence level moderate, strength of recommendation strong)
- *Prophylaxis with antiviral treatment is indicated for liver transplantation from anti-HBc donors to HBV negative recipients.*
  (Evidence level moderate, strength of recommendation strong)
- *For other solid organ transplant prophylaxis is not indicated but may be considered in patients with no previous exposure of hepatitis B.*
  (Evidence level moderate, strength of recommendation strong)

Management Issues in Children Undergoing Solid Organ Transplantation
Children in Transplant Waiting List

HBV-infected children awaiting solid organ transplantation require antiviral treatment to reduce their HBV DNA levels at the time of transplantation. Among the observational studies mentioned in Table 4, for antiviral drugs used in children, LAM was the most widely studied drug

Table 4 Results of Pediatric/Adolescent Studies on Various Nucleos(t)ide Analogs.

Study	Intervention/control	Sample size	Duration	HBeAg clearance	HBV DNA clearance	HBsAg clearance
Lamivudine						
Jonas et al.[145]	LAM	192	52 weeks	26%	23%	2%
	Control	96		15%	13%	0
Ni YH et al.[146]	LAM	29	52 weeks	17%	–	–
	Controls	29		10%	–	–
Hong et al.[147]	LAM	81	52 weeks	60.5%	–	11%
				–	–	–
Liberek et al.[148]	LAM	59	52 weeks	27.1%-		
Koh et al.[149]	LAM	60	24 mo	42%	53%	–
Entecavir						
Jonas et al.[150]	ETV	120	48 weeks	24.2%	49.2%	5.8%
	Control	60		3.3%	3.3%	1.6%
Chang et al.[142]	ETV	9	52 weeks	44%	55.6%	0%
	Control	27		37%	11%	0%
Saadah et al.[151]	ETV	Abstract	24 months	37.5%	37.5%	
Adefovir						
Jonas et al.[152]	ADF	113	48 weeks	15.9%	23%	–
	Control	57		5.3%	0%	–
Jonas et al.[153]	ADF	108	192 weeks	35%	–	–
	Control	54		31.4%	–	–
Chu et al.[143]	LAM + ADF	8	48 weeks	12.5%	100%	–
	ETV only	8		25%	100%	–
	ADF only	11		0%	72.7%	–
Tenofovir						
Murray et al.[144]	TDF	52	72 weeks	21%	89%	2%
	Control	54		15%	0%	0%

Table 5 Post-Transplant Pediatric Studies in Recipients With Anti-HBc Positive Grafts for Prevention of De Novo HBV.

Study	N	Threshold anti HBs (IU/L)	De novo hepatitis B (%)	Follow up (months)
Chang 2003[160]		20	11.1	33.5
Lin 2007[161]	30	100–1000 >1000	15.4 None	57
Park 2008[164]	12	>100	7.1	39
Lee 2016[162]	41	>100	2.2	66
Dong 2017[163]	44	>50	15.91	30

till date but it has low genetic barrier to resistance and is associated with a high risk of virus mutation and resistance. Sokal et al. found YMDD mutation rates of 49% and 64% in second and third years of treatment.[141] This drug has lost favor since the approval of ETV in children >2 years of age. ETV, appears to have best response rates: HBe seroconversion in 24–44% and HBV DNA clearance in 37–55%[142]. There was poor response to ADV monotherapy in LAM resistant children. ETV monotherapy achieved higher seroconversion as compared to ADV (25% vs 0%).[143] There is only one study on TDF in adolescents (12–18 years) with good response (21% HBe seroconversion, 89% HBV DNA clearance).[144] No efficacy or safety based studies have been done on TDF in children less than 12 years of age. Hence for management of HBV infection in the pre-transplant period to reduce the HBV DNA levels, the antiviral of choice is ETV for 2–12 years of age and TDF for those above 12 years of age.

Children Receiving Organs From Anti-HBc Positive Donors

It has been reported from India, that 28.8% of the family contacts of chronic HBV patients[154] and 64% babies of HBsAg positive mothers have occult HBV infection.[155] Although developed countries have much lower prevalence of occult HBV, but there has been increase anti-HBc positive donors in US between 1998 (3.8%) and 2002 (4.9%).[156,157] We can expect much higher prevalence of anti-HBc positive donors in India. Hence keeping the load of occult HBV in mind, all recipients and donors should be tested to determine the status of anti-HBc and HBV-DNA viremia as part of pre-transplant work up in India.

The transplantation of anti-HBc positive livers carries a 25–100% risk of transmitting HBV to recipients[158,159] with 11.1% rate of de novo hepatitis in vaccinated recipients.[160] Usage of HBIG in intraoperative period in the dosage of 100–IU/kg, repeated daily in the same dosage for the first week and then repeating doses of HBIG to keep the anti-HBs titer in the range of 20–1000 IU has shown varying prevalence of de novo hepatitis B from 0% to 15.91% (Table 5). Although the preventive therapy and the threshold levels of anti HBs are not uniform in these studies, the lowest prevalence of de novo hepatitis was seen in children with sustained levels > 1000 IU of anti HBs.[161] In view of

high price of HBIG, a more cost effective strategy of sustaining high titers of anti-Hbs is booster doses of vaccination at around end of first year post transplant when the steroid is either in minimal dosage or stopped.[162] The vaccination doses were found to be 0.8 per year to keep the adequate levels of anti-HBs and the need for HBIG was brought down from 4 booster doses per year to 0.1 booster dose per year.[162] Even ≤3 booster doses post-transplant were enough to allow anti-HBs levels > 1000 IU in 78% of the children who received anti-HBc positive graft.[161] In a more recent pediatric study, preventive therapy was the only significant risk factor for preventing de novo hepatitis which was found in significantly more (P = 0.037) proportions of recipients with anti-HBc positive grafts (7/44) versus those with anti-HBc negative grafts (1/57).[163]

Since presence of anti-HBs antibodies does not guarantee protection against de novo hepatitis in recipients receiving anti-HBc positive grafts, antivirals should be given specially in those who do not attain high titres of anti-HBs despite vaccines. The choice of antivirals should be age appropriate as discussed earlier in this section. Liver grafts from donors with anti-HBc positive are safe in the presence of vaccination and antivirals. Since safety profile of antivirals has not been tested in children < 2 years of age, hence anti-HBc positive grafts should be avoided in this age group.

It is important to acknowledge that we need better identification protocols for children with chronic HBV who are at higher risk for disease progression and/or HCC later in life. More studies are needed to understand the role of age and HBV genotype on response to treatment. Pediatric licensing of newer drugs is urgently needed. Better understanding of indications for treating children with NAs as well as optimal duration of treatment. We have no pediatric studies to see the post-transplant management of overt or occult HBV in recipients. Adult data should be extrapolated for these issues in children.

Consensus Statements

- *HBV positive children in transplant waiting list should receive ETV if they are below 12 years of age and TDF if they are above 12 years of age.*

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(Evidence level moderate, strength of recommendation strong)

- *In children < 2 years, liver from anti-HBc positive donor should be avoided.*

  (Evidence level weak, strength of recommendation strong)

- *Prophylaxis with TDF or ETV (according to patient's age) are recommended when transplanting an anti-HBc-positive liver to an HBV naïve recipient with low titers despite vaccination.*

  (Evidence level moderate, strength of recommendation strong)

- *Post-transplantation HBIG should be given in the first year and HBV vaccination should be given after 1 year preferably maintaining anti-HBs titer of >1000 IU/L.*

  (Evidence level moderate, strength of recommendation strong)

HBV PATIENTS RECEIVING CORTICOSTEROIDS

Corticosteroids are frequently used as chemotherapeutic and immunomodulatory agents in many diseases, including many type of cancers, IBD, Rheumatic disorders, asthma and COPD. They are generally used along with other immunomodulatory or immunosuppressive agents (either simultaneously or sequentially), but they can also be used alone.

Long-term glucocorticoid therapy especially moderate doses of glucocorticoids for more than 3 months have been shown to be associated with an increased risk of HBV reactivation in HBsAg-positive patients.[23] There is a high level of confidence that the true risk of HBV reactivation with long-term systemic corticosteroid therapy is at least 10% when used in HBsAg carriers. The risk of HBV reactivation from long-term glucocorticoid therapy is anticipated to be lower in HBsAg negative, anti-HBc-positive patients[23].

Steroids can be used through various routes like parenteral, oral (conventional steroids and low bioavailability steroids), local (inhaled and intrarticular), and topical (for use on skin, eyes, mucous membranes).

While chemotherapeutic agents in general, especially when given cyclically, have been incriminated, corticosteroid therapy has emerged as a frequent and prominent culprit. The double effects of chemotherapeutic agents that of enhancing replication of HBV during therapy resulting in a high viral load and of immunologic rebound on withdrawal of therapy, are exaggerated with the use of steroid. Other than through its general immunosuppressive effect, steroid also enhances HBV replication through the glucocorticoid-responsive element, which is a transcriptional enhancer inside the HBV genome.[165,166] High dose steroid has also been shown to induce a decrease in both helper and suppressor T-cell function, and increase in primary B-cell function. Four to ten weeks after withdrawal of steroid therapy, there is a rebound of suppressor

T-cell activity without significant changes in either helper T-cell or B-cell function.[167] This mechanism possibly explains HBV reactivation after withdrawal or reduction of corticosteroid treatment, during which an intense rebound of cytotoxic T-cell function may play an important role.

What Dose and Duration of Steroids are Associated with Significant Immunosuppression?

The dose and duration of corticosteroids that are associated with significant immunosuppression are not clearly defined. The Consortium of Rheumatology Researchers of North America evaluated the risk for all infectious events, and found that prednisone use was associated with an increased risk of opportunistic infections (IRR 1.63, 95% CI 1.20–2.21).[168] Second European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease, indicated that doses greater than 20 mg/d of prednisolone in adults are immunusuppressive and increase the percentage of events.[87] The combination of two or three of immunosuppressant drugs enhances the probability of infections.[169]

Reactivation of HBV Due to Steroid Use in HBsAg-Positive Patients

First reactivation was described by Wands et al. in 1975, who described increase in HBsAg titers followed by rise in serum transaminase levels in 85 patients with myeloproliferative disorders and lymphomas receiving chemotherapy, some of whom were initially negative for HBsAg and positive anti-HBs.[170] Another prospective open label cohort study, carried in 41 Chinese adults with idiopathic nephrotic syndrome and low replicative hepatitis B (HBsAg-positive, HBeAg-negative, HBV DNA < 1000 copies/mL), compared standard doses of prednisone (initial dose prednisone 1 mg/kg, then tapered according to response, $n = 22$) vs lower doses of prednisone plus Mycophenolate Mofetil (MMF) (initial dose prednisone 0.5 mg/kg + MMF 0.5 1 g BD, then tapered according to response, $n = 19$)[171]. Without pre-emptive therapy, the risk of reactivation was lower in MMF-prednisone regimen than the group with prednisone in monotherapy (detectable HBV DNA in 36.8% vs 63.6%, $P = 0.047$), reflecting the major effect of higher doses on the HBV reactivation.[171] In one study from South Korea, in patients with asthma and COPD, 198 HBsAg-positive patients who had been treated with only inhaled corticosteroids ($n = 126$) or treated with systemic plus inhaled corticosteroid ($n = 72$), were identified retrospectively. HBV reactivation was more frequent in the systemic corticosteroid group compared with the inhaled corticosteroid group (OR 3.813, 95% CI: 1.106–13.145, $P = 0.032$). Among the patients treated with

systemic corticosteroids, the HBV reactivation rate was significantly higher in those treated for a continuous period of at least 3 months or those who received >20 mg prednisolone per day.[172] Xuan et al. in a literature review in 2014, reviewed 6 articles reporting 144 patients with rheumatological disorders who used steroids, in monotherapy or combined with other therapies.

They found that 20.8% of the patients receiving prednisone experienced HBV reactivation compared to only 4.46 and 9.52% of patients treated with disease-modifying anti-rheumatic drugs or tumor necrosis factor-alpha-blocking agents, respectively.[173] Another retrospective study reported HBV reactivation following at least 6 months of high doses of systemic corticosteroid for connective tissue diseases. Four out of the 98 patients finally had a reactivation after a median time of 10.5 months, and resulted in a mortality of fifty percent[174]. One retrospective study from Israel assessed the risk of HBV reactivation in patients with rheumatic diseases after a 7-day treatment with low to moderate dose of corticosteroids. Reactivation occurred in 8.7% of the treatment episodes. All cases of HBV reactivation were related to administration of biologic agents or additional immunosuppression with anti-metabolites/cytotoxic agents (cyclophosphamide or azathioprine). The results suggested that short episodes of IV corticosteroids seemed to be safe in CHB patients even in the presence of DMARDs, but prophylaxis should be considered for patients exposed to biologicals or cyclophosphamide[175]. Many case reports have also reported HBV reactivations after high dose of steroids in monotherapy[176–178].

In IBD also, there have also been reports of reactivation in patients under corticosteroids, with or without azathioprine or anti-TNF therapy, even resulting in severe acute hepatitis.[179–181] The Spanish REPENTINA study describes 6 cases of HBV reactivation in IBD patients during conventional immunosuppressive therapy, two of them with prednisone in monotherapy. Fifty percent of the cases resulted in liver failure and one of them required a liver transplantation.[182] Although the findings indicate that the risk of hepatitis reactivation is mostly related to high prednisone doses, however, as some cases of HBV reactivation have occurred with low-dose-prednisone therapies, caution is advisable.

The topically acting oral steroids are agents characterized by a low systemic bioavailability due to an important first-pass liver metabolism (e.g. Beclometasone Dipropionate (BDP) and budesonide). So, the typical adverse effects of steroids are partially avoided because of a lower concentration of the drug in plasma. No cases of reactivation of HBV have been described in large studies, although it is not clear how many patients had markers of HBV infection[183]. The intra articular steroid injections have associated with extremely low risk of reactivation.

Reactivation of HBV Due to Steroid Use in HBsAg-Negative, Anti-HBc Patients

In one prospective study from Japan, 45 HBsAg negative, anti-HBc positive and HBV DNA < 2.1 log copies/mL, rhematoid arthritis patients receiving long term immunosuppressives were studied (34 patients received prednisolone, 42 received DMARDs and 42 received biologics). HBV reactivation occurred in only 1 (2.2%) patient after 10 months of low dose MTX and prednisolone treatment.[184] In another multicenter, observational, prospective study over 2 years in patients with resolved HBV infection from Japan, patients with rhematological disorders treated with prednisolone and/or synthetic or biological immunosuppressive drugs with HBsAg negative; anti-HBs positive (≥10 mIU/mL) and/or anti-HBc positive; and HBV DNA PCR negative were enrolled. Among 1042 patients, HBV reactivation was detected in 35 (3.4%) patients (1.93/100 person-years). The risk of reactivation was lower with methotrexate but higher with prednisolone among the different types of immunosuppressive drugs. Of 35 reactivation cases, 8 were on prednisolone only; 7 were on prednisolone along with other immune suppressants; while 21 patients were on other immune suppressants without prednisolone.[94]

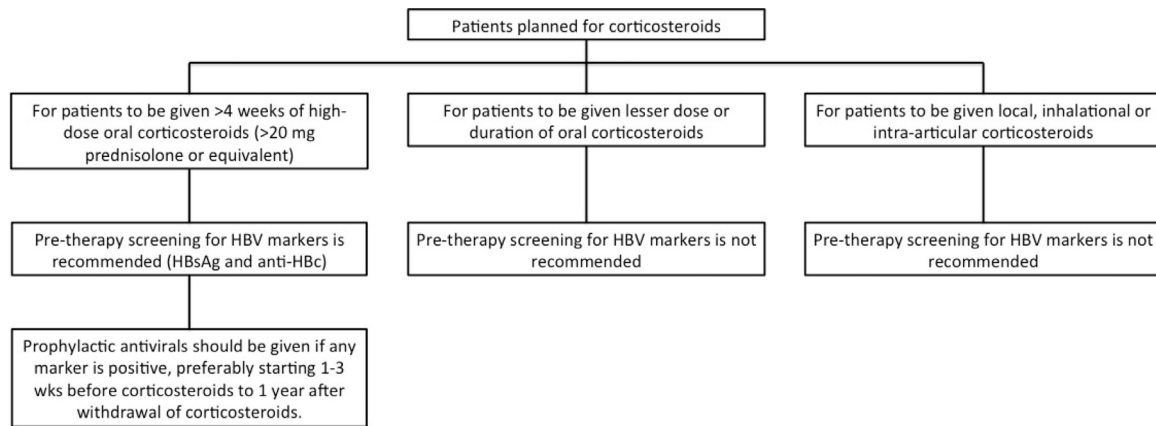Figure 5 shows the algorithm for management of HBV patients receiving corticosteroids.

Consensus Statements

- *For patients to be given >4 weeks of high-dose oral corticosteroids (>20 mg prednisolone or equivalent):*
  - *Pre-therapy screening for HBV markers is recommended (HBsAg and anti-HBc)*
  - *Prophylactic antivirals should be given if any marker is positive, preferably starting 1–3 weeks before corticosteroids to 1 year after withdrawal of corticosteroids.*

  (Evidence level moderate, strength of recommendation strong)
- *For patients to be given lesser dose or duration of oral corticosteroids pre-therapy screening for HBV markers is not recommended.*

  (Evidence level moderate, strength of recommendation strong)
- *For patients to be given local, inhalational or intra-articular corticosteroids pre-therapy screening for HBV markers is not recommended.*

  (Evidence level low, strength of recommendation strong)

HBV IN PATIENTS WITH CKD

The prevalence of HBV infection in patients with CKD on hemodialysis varies from 1 to 10% in developed countries, and up to 20% in Asian countries.[185–187] The incidence of HBV infection in dialysis patients has significantly reduced over the past few decades due to screening of

Figure 5 Algorithm for management of HBV patients receiving corticosteroids.

blood and blood products, strict infection control practices and initiation of widespread vaccination amongst CKD/dialysis patients.[186] The HBsAg positivity rates amongst dialysis patients in India is still very high, ranging between 5 and 13%, as compared to a prevalence between 1.4% and 2.7% amongst non-tribal general population.[1,2,188] This needs to be reduced further and therefore it is important that all dialysis units in India adhere to strict infection control practices as suggested by many available guidelines.[189] This along with other measures has been shown to achieve and maintain a low prevalence of hepatitis B in the dialysis population in many countries over the past two decades.

HBV infection in CKD patients on dialysis can cause chronic liver disease and decreased survival, even though aminotransferase levels and viral activity may remain low for many years. All patients undergoing dialysis are considered high risk for contracting HBV, HCV and HIV, and should therefore be tested for the same on admission to a dialysis unit, and retested at least every 6 months. It is also recommended that all staff members of dialysis units be screened for HBV and accordingly vaccinated, and also have periodic testing of their anti HBs titers to maintain it above 10 μm/mL.[8,186,190] HBsAg is the most widely used screening method to detect the presence of HBV infection. However, the Indian Society of Nephrology recommends that testing for HBV infection in dialysis units should be done using Nucleic Acid Based Testing (NAT), to identify patients in the window period. Though there is no direct evidence in CKD patients, several studies from India have shown that NAT is superior in detection of transfusion transmitted infections, and many countries have now adopted this as standard practice in screening blood donors.[191,192] It may be prudent to consider this as a routine in high-risk areas such as blood banks and dialysis units, though the higher cost may be a limiting factor.

Dialysis patients who are HBsAg negative on initial screening should receive vaccination. Studies in patients on hemodialysis have showed that HBV vaccination

reduced infection rates by 70%.[193] Since patients with CKD and on dialysis are immunocompromised, the rate of seroconversion after standard doses of vaccination may be suboptimal. In a randomized, double-blind, placebo-controlled trial involving 1311 patients receiving hemodialysis, after three doses of HBV of higher strength (40 μg each), only 63% developed anti HBs antibodies. Studies have shown that four doses of vaccine (40 mcg each) gives better a seroprotection rate (73–92%) compared to a conventional 3-dose schedule (45–67%). Patients with CKD who are not on dialysis have good seroconversion with three doses of vaccine, and may need only standard doses of the vaccine (20 mcg) to get the desired result. Therefore, it may be best to screen CKD patients early and initiate vaccination as appropriate.[194–197] Patients on dialysis are recommended to receive four doses of a recombinant hepatitis B, at a higher than standard dose of 40 mcg, at 0, 1, 2, and 6 months.[198] The persistence of immunity hepatitis B vaccine in hemodialysis patients was tested over a 3-year period. Seventy-three percent of patients had an antibody response but by 3 years 41% of these patients lost their antibody. Patients on hemodialysis had lower response rates than the normal population and the response may be transient in many.[199] Annual checking of anti HBs levels and booster doses as needed maybe be prudent in all dialysis patients.

Hepatitis B positive patients with CKD/dialysis should be evaluated for the extent of liver disease and viral activity. This should include ALT level, HBe antigen status, HBV DNA viral load, and presence of significant inflammation and/or fibrosis (by non-invasive methods or liver biopsy). Assessment of the degree of liver fibrosis helps to determine treatment and prognosis. Noninvasive tests such as transient elastography can be used and are particularly useful in identifying those with cirrhosis, but have not been tested much in patients with CKD/dialysis. Liver biopsy can assess both fibrosis and/or inflammation, but carries a higher risk of complications in CKD patients.[41,200] Additional parameters to consider are the

minimal or no increase in transaminases and the lower viral load levels in these patients because of their clearance by dialysis.[201,202]

All HBsAg-positive CKD/dialysis patients should be considered for antiviral treatment if they have HBV DNA levels >2000 IU/mL, significant fibrosis on noninvasive tests (Fibroscan > 8.0 kPa) or moderate inflammation and/or significant fibrosis on histology, irrespective of ALT levels.[8,41,203]

NAs are recommended as the first line of treatment. ETV clears HBV DNA in up to 100% of naive patients at 24 months, with approximate time to undetectability and ALT normalization at a median of 12.6–15.7 months, without any significant toxicity. In LAM resistant patients the response to ETV becomes less with a clearance rate of only 45% at 24 months.[204,205] TDF or TAF is the preferred alternative in LAM resistant patients, with an expected clearance rate of 86% at 96 weeks.[41] Although there is potential nephrotoxicity with the use of TDF, this has not been widely studied in CKD patients. There are however documented reports of chronic tubular damage with hypophosphatemia, and a decline of GFR and bone mineral density in some patients (up to 15%).[206] In renal transplant recipients, TDF appears to be safe and small studies have shown that they were well tolerated with no significant renal toxicity.[207,208] A combination of TDF and telbivudine has been shown to improve GFR and may be considered an alternative in CKD patients and renal transplant recipients; however studies with this combination are limited.[209]

TAF is a promising alternative to Tenofovir disoproxil, both in terms of efficacy and toxicity. Pivotal studies have shown that TAF is non-inferior to TDF for DNA clearance and more importantly had a smaller reduction in creatinine clearance at week 48 and week 96.[210,211] TAF has not been tested in patients with CKD, on dialysis and after renal transplant; however it remains a promising alternative, especially in those with LAM resistant hepatitis B.

All doses of NAs should be adjusted according to eGFR or creatinine clearance values in patients with eGFR <50 mL/min, except for TAF which does not require dose adjustment if eGFR is >15 mL/min. For Creatinine clearance 30 49 mL/min: 300 mg of TDF 300 mg or ETV 0.5 mg should be given every 48 h. For creatinine clearance 10–29 mL/min, TDF 300 mg or ETV 0.5 mg should be given every 72–96 h.

All renal transplant recipients who are HBsAg positive should receive antiviral prophylaxis with NAs (prophylactic therapy, at least two weeks before renal transplant). ETV is the preferred option due to its renal safety, and TDF or TAF can be used in LAM resistant patients. Treatment should be continued indefinitely. HbsAg positive patients with low DNA (less than 2000 IU/mL) with evidence for liver disease or with a high DNA >2000 IU/mL should be treated immediately at the time of diagnosis.

HBsAg negative, anti-HBc positive patients do not require antiviral treatment; they should be monitored for HBsAg reactivation every 6 months and treated only if there is a seroconversion.[8,212]

Consensus Statements

- *All patients with CKD should be screened for HBsAg at diagnosis.*
  - *Patients on hemodialysis should be screened on initiation of dialysis and subsequently every 6 months.*

  (Evidence level high, strength of recommendation strong)
- *All CKD patients who are HBsAg-negative should be vaccinated for HBV.*
  - *CKD patients not on dialysis should receive standard dose (20 mcg) of recombinant vaccine at usual schedule of 0, 1 and 6 months.*
  - *CKD patients on dialysis or those with eGFR < 30 mL/min should double dose (40 mcg) of recombinant vaccine at accelerated schedule of 0, 1, 2 and 6 months.*
  - *Anti-HBs should be checked annually and booster doses should be given when anti-HBs falls below 10 mU/mL.*

  (Evidence level high, strength of recommendation strong)
- *All CKD patients who are HBsAg positive:*
  - *Should be evaluated for extent of liver disease and viral activity, and treatment should be based on standard guidelines for HBV patients.*
  - *NAs (dose according to GFR) are recommended as the first line treatment. TAF, ETV and TDF are the preferred choices.*

  (Evidence level high, strength of recommendation strong)
- *All renal transplant recipients who are:*
  - *HBsAg-positive should receive life-long antiviral prophylaxis with TAF, ETV or TDF*
  - *HBsAg-negative and unvaccinated should receive HBV vaccination with double dose (40 mcg) at accelerated schedule (0, 1, 2, and 6 months). Their anti-HBs titers should be checked 1–2 months after vaccination and re-vaccinated if anti-HBs is below 10 IU/mL.*
  - *HBsAg-negative and previously vaccinated should have annual anti-HBs titers checked and booster doses be given if titers fall below 10 IU/mL*
  - *HBsAg-negative, anti-HBc-positive should be monitored for HBsAg and ALT every 6 months.*

  (Evidence level high, strength of recommendation strong)

CONCLUSIONS

There is a large burden of HBV infection in India. The currently available therapeutic armamentarium for treatment of chronic HBV infection is far from ideal. Apart from poor HBsAg clearance, the biggest hindrance with currently available therapies is persistence of cccDNA, which has significant risk of reactivation. Considering the vast number of patients currently infected or previously exposed to the virus, HBV reactivation in this

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population will remain a vexing and persistent problem. Understanding the cellular and molecular mechanisms involving HBV replication and cccDNA dynamics is pivotal in devising more effective strategies. Recently exciting targets have been identified which definitely hint at better treatment outcomes including achieving the elusive complete cure in HBV infection.

The above INASL guidelines on management of HBV infection in patients receiving chemotherapy, biologicals, immunosupressants, or steroids are the first guidelines on this subject being published from India. We hope that these guidelines will become basis of further research in India so that better quality evidence emerges from India in coming years, and subsequent versions of these guidelines will be more based on Indian data. Considerations for the treatment of HBV in India should include the cost of therapy, socio-economic status, and poor healthcare infrastructure in India. These guidelines will bring some uniformity in the way Indian patients of HBV are being diagnosed, monitored and treated. This uniformity is essential to generate more data on India-specific issues on management of HBV. The current guidance will be updated once more Indian data and newer diagnostic and therapeutic armamentarium become available in India.

CONFLICTS OF INTEREST

The authors have none to declare.

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