



Viral Hepatitis: Manifestations and Management Strategy

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Viral hepatitis is the third most common cause of liver disease in allogeneic transplant recipients and causes significant morbidity and mortality. When treating patients with hematological malignancies, an emphasis should be placed on identification of patients at risk for viral hepatitis with appropriate screening. Initial screening serology should include anti-HCV, HBsAg, anti-HBs, and anti-HBc testing. When hepatitis B exposure has been documented, prophylaxis of viral reactivation for all HBsAg-positive patients with a nucleoside analogue should be implemented. HCV infection appears to have little short-term impact on survival after bone marrow transplantation, but is a

Liver dysfunction is a significant concern in patients receiving chemotherapy or immunosuppressant agents for hematologic malignancies and bone marrow transplantation (BMT). Among the most common causes of liver disease are drug toxicity, veno-occlusive disease (VOD), and liver graft-versus-host disease (GVHD). Furthermore, viruses such as hepatitis B (HBV) and hepatitis C (HCV) are common and can cause significant morbidity and mortality in this population. In allogeneic transplant recipients, post-transplantation viral hepatitis is the third most common cause of liver disease (7-15%), behind GVHD (33-40%) and drug hepatotoxicity (19-30%). In transplant recipients with prior exposure to HBV, the impaired cellular immunity seen in the first 3-6 months can cause reactivation of latent virus and lead to fulminant hepatic failure. However, HCV infection appears to have little short-term impact on survival after BMT, but is a risk factor for VOD and GVHD. In the long-term survivor, HCV infection can lead to significant morbidity and mortality due to the development of cirrhosis, decompensation, and liver cancer. Since effective

risk factor for veno-occlusive disease (VOD) and graft-versus-host disease (GVHD). In the long-term survivor, HCV infection can lead to significant morbidity and mortality due to the development of cirrhosis, decompensation, and liver cancer. Since effective antiviral therapies are available for both hepatitis B and C, routine screening and selected intervention is recommended once reactivation and disease recurrence is documented. In this chapter we will highlight the mechanisms of virus reactivation, clinical manifestations, and management strategies to minimize acute and chronic morbidity in this population.

Antiviral therapies are available for both HBV and HCV, routine screening and selected intervention may offer improved patient survival and limit associated morbidity. In this chapter we will discuss the mechanisms of virus reactivation, clinical manifestations, and management strategies to minimize acute and chronic morbidity in this population.

Hepatitis B

Natural history

Chronic HBV infection affects an estimated 350 million people worldwide including 1.25 million in the United States.¹ In countries with a large immigrant population such as the US, the prevalence of HBV varies, being higher among those who immigrated from high or intermediate prevalence countries and in those with high-risk behaviors such as men who have sex with men, injection drug users, and persons with multiple sex partners. HBV is transmitted by perinatal, percutaneous, and sexual exposure, as well as by close person-to-person contact presumably by open cuts and sores, especially among children in hyperendemic areas. The risk of developing chronic HBV infection after acute exposure ranges from 90% in newborns of HBeAg-positive mothers, to 25% to 30% in infants and children under 5, and to less than 5% in adults. In addition, immunosuppressed persons are more likely to develop chronic HBV infection after acute infection. Fortunately, the incidence of HBV has been in decline worldwide due to the availability of an effective vaccine for the last 20 years.² However, HBV remains a leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma.

Reactivation of HBV infection is a well-recognized complication in infected patients who undergo cytotoxic chemotherapy for cancer. Reactivation of “dormant” infection with an acute hepatitis has been reported in both

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HBsAg-positive and -negative patients treated with chemotherapy or immunosuppression.³⁻⁷ The clinical presentation of HBV reactivation can range from asymptomatic self-limiting hepatitis to severe, potentially fatal progressive hepatitis. Even in patients with evidence of viral clearance and immunity (HbcAb and HbsAb positivity), HBV reactivation may occur and impact on patient outcomes.^{8,9} With the increasing use of potent cytotoxic chemotherapy, reactivation of HBV is becoming a relatively common problem.

Definition, diagnosis, and mechanism of reactivation

The effects of chemotherapeutic agents on HBV were first reported in 1975,¹⁰ and HBV reactivation has been increasingly observed in allogeneic hematopoietic stem cell transplantation (HSCT), with an incidence of 50% or more for susceptible individuals.¹¹ Three distinct groups with prior HBV exposure are at risk for reactivation: (1) chronically infected, viremic patients who develop increases in serum HBV DNA and disease activity during chemotherapy; (2) “chronic, inactive carriers” who are HBsAg positive and HBV DNA negative and convert to active replication during chemotherapy; and (3) patients with immunity against HBV due to past exposure (HBsAg negative, anti-HBs positive and anti-HBc positive) who reactivate with production of HBsAg and HBV DNA. Risk factors that have been associated with disease reactivation include male sex, younger age, prechemotherapy abnormal alanine aminotransferase (ALT), and prechemotherapy HBV DNA above 3×10^5 copies/mL.¹²⁻¹⁵ Also, the degree of immunosuppression and the frequency of chemotherapy have been shown to play a role in HBV reactivation.¹³ Refer to **Table 1** for hepatitis B definitions.

Table 1. Hepatitis B definitions.

Chronic hepatitis B	<ul style="list-style-type: none"> • HBsAg⁺ > 6 months • Serum HBV DNA > 2000 IU/mL (10^4 copies/mL) • Persistent or intermittent elevation in ALT/AST levels • Liver biopsy showing chronic hepatitis
Inactive HbsAg carrier state	<ul style="list-style-type: none"> • HBsAg⁺ > 6 months • HBeAg⁻, anti-HBe⁺ • Serum HBV DNA < 2000 IU/mL • Persistently normal ALT/AST levels • Liver biopsy confirms absence of significant hepatitis
Resolved hepatitis B	<ul style="list-style-type: none"> • Previous known history of acute or chronic hepatitis B or the presence of anti-HBc ± anti-HBs • HBsAg⁻ • Undetectable serum HBV DNA
Reactivation of hepatitis B	<ul style="list-style-type: none"> • Reappearance of active liver disease in a person known to have the inactive HBsAg carrier state or resolved hepatitis B

Reactivation of the virus is typically characterized by elevation of liver transaminases, newly detectable or increasing HBV DNA levels in the serum, and clinical hepatitis.⁷ It is best defined by the occurrence of hepatitis during or after cytotoxic chemotherapy accompanied by an increase/detection of HBV replication from a low to a high virus level (≥ 10 -fold increase) in patients with chronic or past HBV infection.¹⁶ The mechanism by which this reactivation occurs is poorly characterized but likely involves a two-stage process.¹⁶ There is an initial stage of activated or enhanced viral replication during the cytotoxic or immunosuppressive therapy. This is characterized by the detectability or dramatic increase in HBV DNA replication, HBeAg release in the serum, and active infection of hepatocytes with HBV and continuing replication. The viral reactivation is likely due to the suppression of immune mechanisms that normally serve to control viral replication. The second stage occurs following the withdrawal of the cytotoxic or immunosuppressive agents, with restoration of the immune function (T-cell-mediated response) and resultant immune-mediated destruction of infected hepatocytes. This immune reconstitution phase is usually characterized by a clinical hepatitis with transient elevation of ALT, possible jaundice, and the development of constitutional symptoms.

Clinical manifestation and consequences

The clinical picture that results as a consequence of HBV reactivation is one of acute hepatitis that can even progress to severe and fatal liver damage. The timing of the reactivation in HSCT patients varies, but is most common within the first 2-3 months in HBsAg-positive patients and is a much later onset (median 19 months) for those who are anti-HBs positive.¹⁷ The delayed onset of viral reactivation in those with resolved infection is probably a result of immunosuppression-induced decline in recipient-derived immunoglobulin over 1-2 years after HSCT. However, with more use of therapeutic monoclonal antibodies against B and T lymphocytes, an increasing incidence and earlier timeline of HBV reactivation in anti-HBs patients is likely. About half of HBV carriers (HBsAg-positive) that undergo chemotherapy will develop some elevation of liver transaminases and 10% will become jaundiced. The fatality rate from patients that develop icteric hepatitis with HBV reactivation is between 5% and 40%.¹⁴ Those patients with evidence of cirrhosis are more likely to decompensate and develop jaundice, ascites, and hepatic encephalopathy. There are also some rare reports in HBsAg-positive BMT recipients of fibrosing cholestatic hepatitis, which is a rapidly progressive cholestatic hepatitis and carries high mortality among BMT recipients.¹⁸ One of the other important consequences of HBV reactivation is that it often leads to premature termination of chemotherapy or disruption in treatment schedules, which can impact patient survival.

Strategies of management and prevention of reactivation

Prevention of HBV infection or reactivation should be the goal of treating patients with hematologic malignancies or in BMT recipients. Although steroid-free regimens have a lower cumulative incidence of HBV reactivation, they are not appealing due to a lower rate of remission and worse survival.¹⁹ Use of preemptive interferon administered at initiation of chemotherapy for lymphoma was reported by Leaw and colleagues to be a promising approach to prevent HBV reactivation, but interferon is associated with significant side effects (including myelosuppression) and many patients are not candidates.²⁰ Nucleoside analogues have become widely accepted for prophylaxis of reactivation of HBV in clinical practice and are supported by prospective trials in patients undergoing chemotherapy.^{3,4,20,21} In these studies, prophylactic lamivudine dramatically reduced the chances of reactivation (from 24-53% to 0-5%) and also led to improvement in survival free from hepatitis.^{22,23} In HSCT patients, preemptive use of lamivudine in all positive donors and recipients, as well as HBV vaccination in HBsAg-negative recipients, has significantly reduced the risk of HBV hepatitis and liver failure.²⁴ In addition, for the patient that develops active HBV infection, lamivudine has also been effective in controlling viral replication and allowing many patients to continue chemotherapy.¹⁴

The optimal duration of lamivudine or other nucleoside analogues in the preemptive setting is unknown. Most trials and case series have continued therapy for at least 4-8 weeks beyond the completion of immunosuppression or chemotherapy. Treatment may need to be extended for longer periods for those patients at higher risk of reactivation: i.e., those receiving HSCT, anti-B or anti-T cell therapy, or evidence of prechemotherapy active HBV replication. Also, all patients should be monitored for a possible flare after nucleoside antiviral therapy is withdrawn, especially those with high pre-chemotherapy HBV DNA replication ($\geq 10^4$ copies/mL).⁴ In fact, for those patients who have chronic HBV infection with significant active replication (HBV DNA $> 10^4$) prior to chemotherapy, long-term antiviral therapy with a nucleoside analogue is likely to be indicated.

Lamivudine has some important limitations, including a high incidence of treatment-resistance due to mutations (24% at 1 year of therapy and 60% at 3 years)²⁵ and potential flares of HBV hepatitis upon drug discontinuation.²⁶ Other nucleoside analogues (adefovir and entecavir) are also approved for the treatment of chronic HBV infection, including patients that have developed lamivudine resistance. However, limited clinical data are available on these drugs in the prevention of HBV reactivation, but they have very appealing profiles and should be effective.^{27,28} Recently, adefovir has been reported to have good safety and efficacy in HBV reactivation for both primary and lamivudine resistant HBV.²⁹ Both adefovir and entecavir have similar or superior antiviral activity to lamivudine

and much lower rates of resistance ($< 5\%$) at 1 year.^{30,31} Therefore, these drugs have some advantages when compared to lamivudine, and provide a good alternative for preventing HBV reactivation, especially in patients requiring long-lasting immunosuppression or during repeated courses of chemotherapy.

In summary, all patients that will receive chemotherapy and especially patients that will undergo HSCT should be screened for HBV infection prior to the initiation of immunosuppressive therapy. Any HBsAg-positive patient should receive appropriate prophylaxis with a nucleoside analogue throughout chemotherapy and for at least 3 months after chemotherapy is completed. This strategy has clearly been shown to decrease the incidence and morbidity of HBV reactivation. For those patients who have previously resolved HBV infection, the data are less clear, and close observation with targeted therapy only for those with documented reactivation is a reasonable option. See **Table 2**.

Hepatitis C

Natural history

Approximately 3% of the world's population is infected with HCV, and it is estimated that, in the United States alone, 12,000 people die annually of HCV-related complications including liver failure or cancer.³² Unlike HBV, the majority of adults will develop chronic infection after exposure to HCV and, since it is an RNA virus, there does not appear to be a latent or dormant phase of viral replication. While the incidence of acute HCV infection is now very low, it is not uncommon for patients to come to transplantation already infected. It is also well established that HCV recurrence after solid-organ liver transplant is nearly universal and results in progressive fibrosis, cirrhosis, graft loss, and the potential need for re-transplantation.³³ Indirect evidence suggests increasing immunosuppression likely worsens HCV disease progression, leading most transplant programs to limit immunosuppression use as much as possible in HCV⁺ patients. The validity of this approach

Table 2. Summary of hepatitis B virus (HBV)-related Issues.

- HBV reactivation is a common complication in HBsAg-positive and HBcAb-positive patients undergoing immunosuppressive anticancer therapy
- Prophylactic therapy with nucleoside analogues has been shown to significantly decrease the incidence and morbidity of HBV reactivation
- HBsAg positive patients should begin prophylactic antiviral therapy before chemotherapy and continue at least 3 months after the end of chemotherapy
- For HBsAg-negative patients who have evidence of previous infection (HBcAb-positive), either prophylactic antiviral therapy or close monitoring with targeted therapy is suggested
- HBV vaccination is recommended for all HBsAg-negative recipients prior to hematopoietic stem cell transplantation

has yet to undergo rigorous evaluation and is formed based on mainly observational and retrospective reports.

The impact of HCV infection on the outcome of bone marrow transplants, patients undergoing chemotherapy and other immunosuppressants is unknown. Various studies have demonstrated a slight increased incidence of liver test abnormalities, VOD, and liver failure in bone marrow recipients with pretransplant HCV infection compared to those without evidence of previous infection.³⁴ The prevalence of HCV infection in patients with B-cell non-Hodgkin lymphoma and other lymphoproliferative disorders is between 8% and 32% and presents a significant management concern in these patients,³⁵ especially given the rare cases of liver failure that have been reported.^{36,37} However, the reality is that hepatic dysfunction, clinical hepatitis flares, and fulminant hepatic failure are very uncommon events in HCV-infected patients who receive chemotherapy when compared to HBV-infected patients.

Mechanism of disease reactivation

It is known that immunosuppression enhances HCV viral replication, likely secondary to impairment of cellular immunity. Typically, the outcome of HCV infection is determined by the interaction between the virus and the host immune system. HCV-specific immune response in the immunosuppressed patient seems to be less efficient or of lower strength compared with normal patients. Potential reasons for this observation include immunosuppression or impairment of dendritic cells and other immunocompetent cells. However, in BMT patients there is minimal evidence of HCV disease re-activation early after transplant, although the long-term impact can be more significant.³⁸ As seen in HBV reactivation, withdrawal of cytotoxic or immunosuppressive drugs will lead to restoration of the immune system with a potential increase in immune-mediated destruction of hepatocytes and active hepatitis.³⁹

Clinical manifestation and consequences

Aminotransferase elevation is not seen immediately post-transplant and is more likely to occur 2-3 months later, when the immunosuppression for GVHD is tapered and the cellular immunity returns. In a study by Zuckerman et al, HCV patients did not demonstrate a higher incidence of severe hepatic dysfunction during chemotherapy for malignancies compared to HCV-negative patients. In those with positive HCV infection the chemotherapy was not associated with jaundice, fulminant hepatitis or deaths.³⁹ However, liver test abnormalities during therapy are very common and seen in 54% of the HCV-positive patients and in 34% of the HCV-negative patients. In seven different studies of bone marrow transplantation, liver test elevation has been reported in up to 85% of the patients with HCV infection prior to transplant.³⁴ Hepatitis C infection is also one of the risk factors for VOD of the liver, also known as sinusoidal obstruction syndrome. The reported incidence of VOD in these studies was 14% of those infected with

HCV prior to transplant compared to 8% of the patients without HCV.³⁴ Chronic liver inflammation in HCV-infected patients may cause endothelial cell membrane changes of hepatic sinusoids or hepatocytes, which, when associated with the drug action, may stimulate the formation of microthrombi, thus triggering VOD.⁴⁰ Since it is often difficult in an HCV-positive patient to discriminate the etiology of ALT elevation (drug, GVHD, VOD, HCV, etc.), a liver biopsy is often required.

As previously highlighted, there is no significant short-term impact of HCV on outcome after BMT. Nevertheless, the long-term impact of chronic HCV infection can be deleterious in the liver, causing significant fibrosis progression, liver failure and increased risk of hepatocellular carcinoma. One group has recently reported a more rapid rate of fibrosis progression after BMT, with median time to cirrhosis of 18 years, as compared to 40 years seen in the control group. HCV disease progression ranked third, behind infections and GVHD, as a cause of late death after BMT.⁴¹ Long-term survivors after BMT thus appear to be at higher risk for HCV-related complications and treatment of HCV becomes critical.

Strategies of management and prevention of disease reactivation

Therapy for HCV infection in patients with hematologic malignancy can be considered once a patient's immunity and bone marrow have recovered, immunosuppressive drugs have been stopped, and there is no evidence of GVHD. Although very little literature exists of treatment of chronic HCV in patients with BMT, a recent study highlights the efficacy of combination therapy with pegylated interferon and ribavirin. Combined therapy led to a sustained virological response (undetectable HCV RNA 6 months off therapy) in 20% of the patients; however, 30% of the patients were not treatment candidates due to contraindications.⁴² Typically, the major contraindications for treatment include uncontrolled depressive illness, autoimmune hepatitis, untreated hyperthyroidism, pregnancy, severe chronic illness (heart failure, COPD, coronary artery disease, poorly controlled diabetes) and following heart, lung and kidney transplant.⁴³ Overall, antiviral therapy for HCV in immunocompromised patients (HIV, transplant, etc.) is often associated with poor response rates, which highlights the need to stratify the risk-versus-benefit ratio of treating these patients. Histological liver evaluation should be performed in all patients to evaluate the stage of fibrosis and grade of necroinflammation. Patients with more advanced disease who are at risk of progression to cirrhosis and its complications should be targeted for therapy. In recipients with HCV infection and marked fibrosis or cirrhosis, myeloablative therapy and HSCT is often contraindicated due to the increased risk of VOD, multiorgan failure and death.⁴⁴ Thus, a liver biopsy should also be considered in all patients with known HCV prior to HSCT.

Another concern is the potential transmission of HCV

from an HCV-positive donor. The prevention of HCV transmission in transplantation has made great strides since the introduction of HCV screening in 1990. With the refinement of diagnostic assays, the incidence of post-transfusion HCV hepatitis has been reduced to less than 0.3%. However, post-transfusion HCV hepatitis remains a problem in many parts of the world where donor screening has not been systematic and where contaminated instruments have been used in blood procurement, mass immunization, and surgical/dental procedures. Currently, the major identifiable risk is intravenous drug use with contaminated needles. With the lack of an effective HCV vaccine, pre-exposure prophylaxis is not possible. Since the introduction of donor screening in 1990, the plasma pools for hepatitis B immunoglobulin and hyperimmunoglobulin are devoid of anti-HCV antibodies and hence not likely to be effective for postexposure prophylaxis. Thus, if the donor is anti-HCV positive, the only way to prevent possible HCV transmission to the recipient is to treat the donor with antiviral therapy to achieve undetectable levels of the virus before the harvest. Typical treatment regimens for HCV include 48 weeks of therapy with interferon and ribavirin, resulting in cure rates of approximately 40-50%. See **Table 3**.

Summary

The lessons for health care providers prescribing chemotherapy, particularly for patients with hematological malignancies are clear: (1) emphasis should be placed on identification of patients at risk for viral hepatitis with appropriate screening, which includes anti-HCV, HBsAg, anti-HBs, and anti-HBc serologies; (2) prophylaxis of viral reactivation for all HBsAg-positive patients with a nucleoside analogue; (3) antiviral therapy when viral reactivation is detected in those not receiving prophylaxis; (4) close monitoring of liver disease activity during and after chemotherapy for patients with HBV and HCV infection; and (5) targeted antiviral therapy in long-term HCV survivors.

Table 3. Summary of hepatitis C virus (HCV)-related issues.

- HCV infection is common in stem cell recipients (5-70%)
- Ongoing or previous infection with HCV is not a contraindication for bone marrow transplantation (BMT)
- HCV infection is associated with increased susceptibility to veno-occlusive disease (VOD) and graft-versus-host disease (GVHD), but does not appear to impact 5- to 10-year survival
- Fibrosis progresses more rapidly in the setting of BMT and liver-related mortality is the third leading cause of late death
- Selected long-term survivors should be considered for antiviral therapy
- Pegylated interferon and ribavirin can be safely administered to patients who have been off immunosuppression for > 6 months and who have no evidence of GVHD or myelosuppression

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