NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Hepatitis B Reactivation Guideline

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Approval Group:	GGC Viral Hepatitis Managed Clinical Network

Important Note:

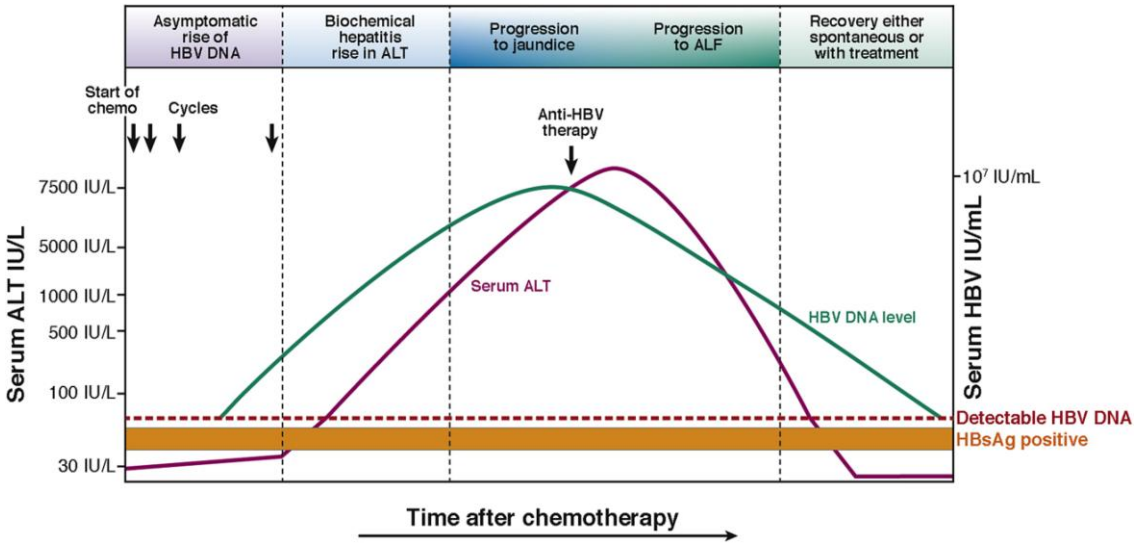
The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

NHS GGC Hepatitis B Reactivation Guideline November 2020

Hepatitis B virus reactivation (HBVr) refers to the abrupt increase in hepatitis B virus in patients with minimally active or resolved/cleared HBV infection. The loss of HBV immune control can lead to an increase in or the reappearance of HBV DNA and a rise in ALT. Liver damage due to HBVr may occur during immunosuppression and/or following immune reconstitution. HBVr may be subclinical or rarely may progress to liver failure or death despite antiviral therapy.

Onset of HBVr

The timing of onset of HBV reactivation is variable depending on the host status, underlying disease, and the type of immunosuppressive therapies. It may occur as early as within the first 2 weeks of onset of chemotherapy or more than a year after the cessation of immunosuppression.



For most patients there is an asymptomatic phase early in HBV reactivation that provides a window of opportunity to initiate treatment. In HBsAg-positive patients, this asymptomatic phase is characterized by a rapid increase in HBV-DNA level, which is followed by a rapid increase in serum ALT level. In HBsAg-negative patients, this asymptomatic phase is characterized first by the reappearance of HBsAg and then sudden increase in HBV-DNA level, followed by an increase in serum ALT level. Some patients may progress to acute liver failure characterized by an increase in bilirubin, prothrombin time, development of ascites, and hepatic encephalopathy.

Who is at risk?

Hepatitis B virus carriers (HBV surface Antigen (HBsAg) positive) and those with “resolved” or “cleared” HBV infection, are at risk of HBV reactivation on receiving some chemo or immunosuppressive therapies. “Resolved” HBV infection describes patients who are HBsAg negative but HBV core antibody (anti-HBcore IgG) positive which is evidence of previous infection. Even after loss of HBsAg, HBV genetic material remains inside hepatocytes, and serve as a template for future viral replication. Reactivation is much more common in HBV carriers than those with “resolved” HBV infection.

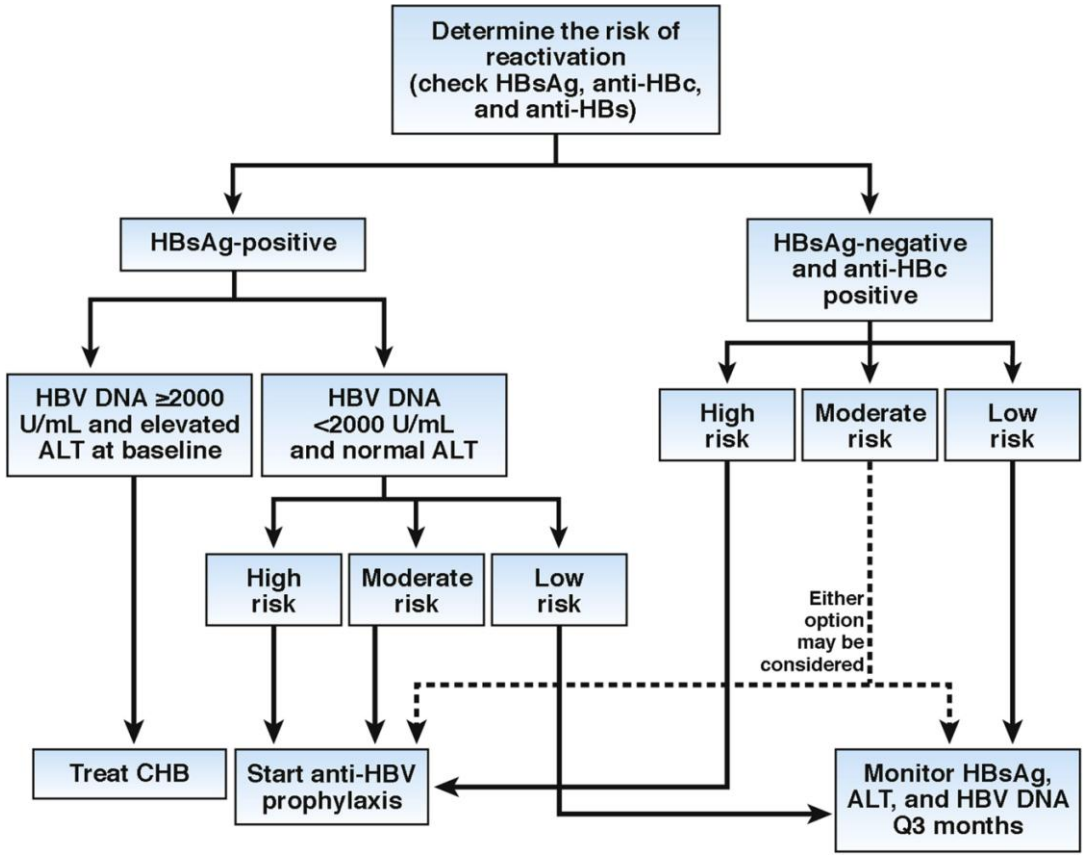
Management of patients at risk of HBV reactivation

Patient at potential risk of HBVr if given immunosuppressive therapy should be discussed with Infectious Diseases, Hepatology or Virology in advance of starting immunosuppression.

Two strategies are used for patients at risk of HBV reactivation

- Prophylactic treatment with antiviral therapy or
- Monitoring of HBsAg, LFTs and HBV DNA and start treatment if required

The strategy chosen will depend on the risk of reactivation for that individual based on their screening results, and the type of immunosuppression planned. Patients with occult HBV (HBsAg negative, anti-HBcore IgG positive but with repeatedly detectable HBV DNA) should be managed as if they are HBsAg+. Occult HBV is rare.



For HBsAg negative, anti-HBcore IgG positive patients, treatment should be started if HBsAg seroreversion occurs or HBV DNA becomes detectable, irrespective of ALT levels.

HBsAg positive carriers / Occult HBV

Moderate to High risk of HBVr:

- Cancer chemotherapy
- Bone Marrow and Solid organ transplant
- B cell–depleting agents (eg, rituximab)
- Anti-TNF agents
- Other monoclonal immune-modulators
- 10mg Prednisolone daily for 4 weeks

The EASL guideline recommends that these patients should be urgently referred to a specialist clinic and start Entecavir or Tenofovir as a treatment / prophylaxis before starting immunosuppression (if possible). In many cases these patients will already be attending HBV clinics and may already be on treatment.

Where baseline renal function is deranged, in renal transplant patients or if treatment carries a high risk of nephrotoxicity (due to tumour lysis syndrome or nephrotoxic regimes) entecavir or tenofovir alfenamide (TAF) may be the preferred option. Note, TAF is not licensed for HBV treatment in Scotland.

HBV treatment should continue for at least 12 months (18 months for rituximab-based regimens) after cessation of the immunosuppressive treatment and discontinued only after review by ID or Hepatology. For many patients HBV treatment will continue until for their chronic hepatitis B.

Low Risk of Reactivation (<1%):

- Azathioprine, methotrexate
- Intra-articular corticosteroids
- Oral corticosteroids daily for 1 week

No specific treatment is required, but HBV reactivation should be considered if the patient presents unwell or there is an unexplained rise in ALT.

HBsAg negative and Anti-HBcore IgG positive with undetectable HBV DNA "Resolved Hep B Infection"

High risk of HBVr (10%+)

This includes:

- Patients receiving Rituximab
- Bone marrow or stem cell transplant recipients

Treatment (prophylaxis) with Entecavir, Tenofovir or Lamivudine is recommended for these patients. They do not necessarily need to be seen in an ID or Hepatology clinic, but can be discussed by phone or email to decide the best treatment option. Treatment (prophylaxis) should continue for the duration of Rituximab therapy and at least 18 months afterwards. Monitor LFTs and HBsAg (+/- HBV DNA) every 3 months throughout treatment and continue for at least 12 months *after* prophylaxis withdrawal.

Low Risk and Moderate Risk of Reactivation (<1 % - <10%)

Worldwide, 2 billion people have evidence of past exposure to HBV (HBsAg negative and anti-HBcore IgG positive). Few of these patients are at risk of HBV reactivation and for most, monitoring and **not** prophylaxis is generally recommended.

Solid organ transplant recipient's e.g. renal transplant, are at a low risk of HBVr and monitoring only is recommended for this group.

Monitor LFTs and HBsAg (+/- HBV DNA) every 3 months during and for 12 months after immunosuppression. Requests to the virology lab should indicate that the patient is on immunosuppressive therapy. Do not repeat anti-HBcore IgG testing.

If HBsAg seroreversion occurs or HBV DNA becomes detectable, discuss with ID or Hepatology and start entecavir, tenofovir or TAF irrespective of ALT levels.

For selected clinical settings, characterised by long duration of immunosuppression, limited compliance to monitoring or unknown risk of viral reactivation e.g. with newer biological agents, prophylaxis, rather than monitoring, may be recommended. Discuss with ID, Hepatology or Virology.

Consider also prophylaxis in patients with established cirrhosis given the clinical consequences if HBVr did occur.

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Risk of HBV Reactivation

The risk of reactivation can be divided broadly into:

- High risk (if the rate of HBV reactivation is >10%)
- Moderate risk (if the risk of reactivation is between 1%–10%)
- Low risk (if the risk of reactivation is <1%)

In general, the more immunosuppressive the regimen, and the longer the duration of treatment, the higher the risk of HBV reactivation. The figure below indicates relative risks of different treatments.

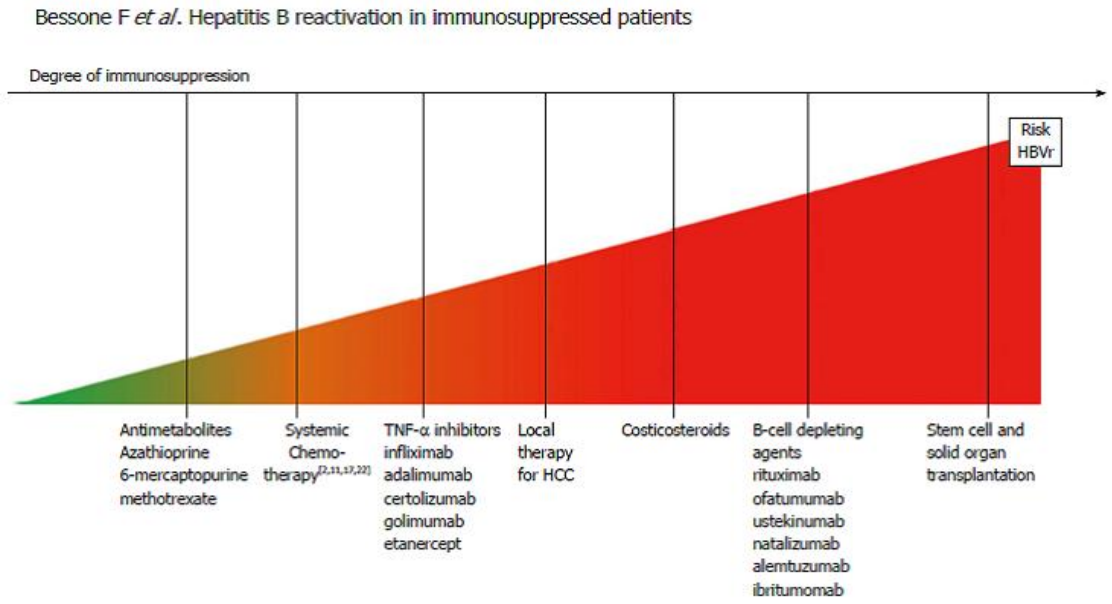

Figure 2 Immunosuppressing agents and related risk of hepatitis B reactivation. HCC: Hepatocellular carcinoma; TNF-α: Tumor necrosis factor-α; HBVr: Hepatitis B virus reactivation.

Stem cell transplantation

HBVr occurs in around 50% of HBV carriers (HBsAg positive) and 10% of those with "resolved" HBV infection (HBsAg negative and anti-HBcore IgG positive). Due to the considerable delay in immune system reconstitution that typically occurs, the risk of HBVr can continue for several years after transplantation.

Solid organ transplantation

HBVr risk has been known to reach 50% in HBsAg-positive patients after kidney transplantation. The risk is much lower in those with resolved HBV, <5%.

Biologics / immuno-modulatory therapies

The risk is thought to be moderate for most of these therapies, though many of these are new with little clinical experience available. See the 2017 Gastroenterology paper in the references for further reading.

Rituximab
This is a monoclonal antibody directed against B Cells used to treat several haematological malignancies and some rheumatological conditions. Reactivation is common in both HBV carriers and those with resolved HBV infection (up to 25%) and may occur months after treatment

Tumour necrosis factor-α inhibitors
Anti-TNF-α agents are approved to treat rheumatoid arthritis, intestinal inflammatory diseases and psoriasis, e.g. infliximab, adalimumab, certolizumab, golimumab and etanercept. Comparative risk assessment between these agents is not possible. Estimated risk of HBVr during anti-TNF-α monotherapy is between 1% and 10% in HBsAg+ carriers, and lower in isolated anti-HBcore IgG+ patients.

Tyrosine kinase inhibitors
Level of risk currently unknown but European Medicines Agency recommends screening for HBV prior to treatment and close monitoring for HBVr during and after treatment

Cancer Chemotherapy

- **Haematological malignancy** - Reactivation occurs in up to 50% of HBsAg+ patients and in up to 10% of anti-HBcore IgG+ patients receiving chemo. The risk is higher with Rituximab and high doses of steroids
- **Solid tumour** - Breast / lung / colon cancer: HBVr risk 10-30% in HBsAg positive patients. Low risk for anti-HBcore IgG+ patients.

Steroids – risk is related to dose and duration

- **High risk** (> 10% risk of HBVr) - HBsAg positive patients who receive > 10 mg/daily of prednisone for 4 weeks or longer
- **Low risk** (< 1% risk of HBVr): anti-HBcore IgG positive patients treated with <10 mg/daily of prednisone for less than 4 wk and patients with local steroid treatment (such as intra-articular infusion)

Antimetabolites
Methotrexate, azathioprine, cyclosporine present a low risk of HBVr

Hepatitis C Co-infection
In patients with HCV-HBV co-infection, the HBV DNA level is often low or undetectable. There is a potential risk of HBV reactivation during or after HCV clearance. For HBsAg positive patients, current EASL guidelines recommend HBV prophylactic treatment during the duration of Hep C treatment and at least until week 12 post anti-HCV therapy. In patients who are HBs antigen-negative but anti-HBc antibody-positive, serum ALT levels should be monitored to detect possible reactivation and both HBs antigen and HBV DNA should be tested if ALT levels do not normalise or rise during or after anti-HCV therapy.

Screening Prior to Immunosuppression

Patients who are to be given immunosuppressive therapies should be screened prior to starting therapy. These would include:

- Transplant recipients – haematological and solid organ
- Cancer Chemotherapy patients
- Rheumatology / Gastroenterology/ Dermatology patients due to receive biologic or other immunosuppressive therapies. Examples of conditions where these may be used include SLE, Rheumatoid arthritis, vasculitis, psoriasis, inflammatory bowel disease, autoimmune hepatitis

The rationale for screening for HBV prior to immunosuppression is to allow antiviral therapy to be started pre-emptively, or to adopt a strategy of monitoring and starting therapy if HBVr occurs. In GGC, HBV infection is most common in patients from SE Asia, India, Pakistan and sub-Saharan Africa. Many patients are unaware of their HBV status. The EASL guidelines recommend screening all patients and not just those deemed at higher risk of HBV infection.

Screening in NHS GGC

OnTrakcare, request:

- **Hep B screen - HBsAg - current infection**
- **Hep B - anti-HBc IgG – past infection**

Indicate on the request form that patient is to start immunosuppressive therapy. This alerts the virus lab so that **HBV DNA** is also tested in patients found to be positive for anti-HBcore IgG.

- **HBsAg** detection indicates chronic hepatitis B carrier status. Rarely a low level of HBsAg is detected in patients who do not have HBV but have recently received HBV vaccination. If possible, take blood tests for HBsAg prior to vaccination.

- **Anti-HBcore IgG** detection in patients who are HBsAg negative indicates past exposure to HBV which is now resolved or cleared. Rarely the result is a false positive due to recent administration of blood products to the patient. Repeating the anti-HBcore IgG with other markers for HBV may clarify the situation. This can be arranged following discussion with the virology lab.

- **HBV DNA** detection indicates current HBV infection. Rare HBV DNA at very low levels is detected in HBsAg negative patients. This may be due to lab contamination or rarely due to *occult* HBV. Discuss with the virology laboratory.

For questions regarding screening or laboratory results, contact the Virus Lab:

Monday-Friday 9an-5pm- 0141 201 8722

Email address: west.ssvc@nhs.net

Screening Donors and Recipients prior to Organ transplantation

In the setting of organ transplantation there is also the potential risk of HBV infection from the donor organ itself if it comes from a donor with prior exposure to HBV.

All donors and recipients should be screened for HBsAg and anti-HBcore IgG. Recipients who are non-immune to Hepatitis B should be vaccinated, preferably prior to transplantation. Higher dose vaccine may be required. Ensure anti-HBs titres are checked regularly.

Management of Organ Recipients from HBsAg negative, anti-HBcore IgG positive donors

HBsAg positivity is usually a contraindication to the use of organs, but may still be considered for life-saving (as opposed to life-modifying) transplantations. Organ donation from HBsAg negative, anti-HBcore IgG positive donors is more common. The management of liver transplants from these donors is beyond the scope of this guideline and should be discussed with Virology.

For Renal and other non-liver transplantation, the following is taken from the American Society of Transplantation guidelines.

The risk of transmission is influenced by the recipient immunity and possibly by prophylaxis. HBV vaccination with anti-HBs titres > 10IU/L has been shown to be protective for renal transplant recipients of anti-HBcore positive donors. Similarly the risk of transmission from anti-HBcore positive heart and lung donors has been found to be low (0-3%). Importantly, the largest single study reported from the United Network for Organ Sharing database has shown no difference in 5-year adjusted mortality rates for recipients of anti-HBc positive donors. Due to the low risk lamivudine may be considered but Hep B Immunoglobulin (HBIG) is not recommended.

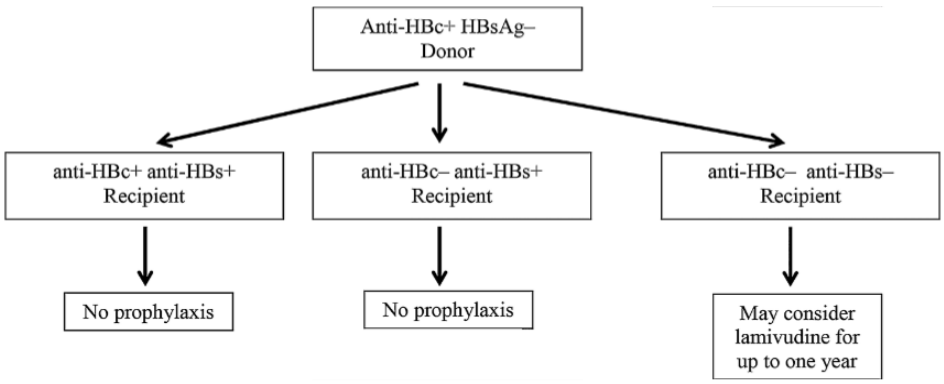

Figure 2: Algorithm for use of non-liver grafts from anti-HBc+ donors in recipients without chronic HBV.

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