NHS
Gloucestershire Hospitals
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Hepatitis B prophylaxis in adults taking immunosuppressive therapy

Background

People with current Hepatitis B Virus (HBV) infection and past HBV exposure who require immune-suppressive medications are at risk of HBV reactivation. Solid organ transplantation, chemotherapy, immune-suppressive and immune-modulating drugs for the treatment of autoimmune diseases are leading causes of HBV reactivation (NICE, 2017). HBV reactivation carries a risk of acute liver failure and death in some cases. Hence, formal, individualised, specialist assessment is needed to determine the risk of HBV reactivation; patients at high risk will require antiviral therapy as prophylaxis under the guidance of a specialist viral hepatitis service.

People with past HBV exposure are considered to be low complexity patients who are able to receive their HBV prophylaxis and monitoring under the umbrella of their referring specialities with some guidance. This pathway sets out the process for existing and new patients that fall within this category.

Scope

This guideline will cover the indications for HBV prophylaxis in patients prescribed chemotherapy/immunotherapy with past HBV exposure.

Audience

All clinical staff in Gloucestershire Hospitals NHS FT involved in the care of patients requiring HBV prophylaxis.

Derogation from NICE Guidance

There is no up to date NICE guidance for HBV prophylaxis in surface antigen negative patients but the European Association for the Study of the Liver (EASL) guidelines (2017) state:

- All candidates for chemotherapy and immunosuppressive therapy should be tested for HBV markers prior to immunosuppression
- All surface antigen positive patients should receive entecavir or tenofovir as prophylaxis
- Surface antigen negative patients should receive prophylaxis if they are at high risk of reactivation
- Prophylaxis should continue for at least 12 months after stopping immunosuppression and monitoring should continue for at least 12 months after prophylaxis withdrawal

Identification of patients

Prior to initiation of immunosuppressive therapies, patients should be screened for past exposure to Hepatitis B (HBV) to identify those at risk of reactivation. Bloods required are: HBV surface antigen (HBsAg), HBV core antibody (HBcAb or anti-HBc), HBV DNA/HBV viral load, and HBV surface antibodies (HBsAb).

At baseline screening, request HBcAb and HBsAg (gold bottle). If HBcAb is positive and HBsAg is positive, request HBV DNA/HBV viral load (2 x EDTA).

Patients with past HBV exposure

Table 1 highlights the serological markers in patients with past HBV exposure. In these patients there is no current circulating HBV DNA or surface antigen.

Table 1. Serology of patients with past HBV

Serological marker	Target patient profile	Description
Surface antigen (HBsAg)	Non-reactive	The absence of surface antigen indicates no evidence of current HBV infection
Core Antibody (HBcAb or anti-HBc)	Reactive	Exposure to HBV, this is present in past and current infection
HBV DNA/HBV viral load	Not detectable	Represents the direct product and hallmark of viral replication.
Surface antibodies (HBsAb)	Reactive or non-reactive	Surface Antibody is present in past HBV infection but is not always present

Patients with current HBV infection

Patients who are HBsAg positive are at higher risk of reactivation, where the levels of HBV DNA (viraemia) become significantly increased and patients should be referred to the viral hepatitis nurses.

Table 2. Serology of patients with current HBV

Serological marker	Target patient profile	Description
Surface Antigen (HBsAg)	Positive	The presence of surface antigen indicates current HBV infection
Core antibody (HBcAb or anti-HBc)	Reactive	Exposure to HBV, this is present in past and current infection
HBV DNA/HBV viral load	Can be undetectable but often detectable	Represents the direct product and hallmark of viral replication and is a reliable indicator of active infection
Surface antibodies (HBsAb)	Non-reactive	Surface antibodies are generally not present in this group

Patients at risk of contracting HBV

Consider HBV vaccination for HBcAb -ve, HBsAg -ve patients who are at risk of contracting HBV. Ensure patients are aware of the risk factors for HBV. The HBV vaccine should be arranged by primary care. The immune-suppressive agent does not need to be postponed until the vaccine is administered.

Immune-suppressive agents by class and the risk of HBV reactivation

Tables 3 and 4 set out the risk of HBV reactivation for HBsAg positive and HBsAg negative patients with various classes of immune-suppressive agents. Risk factors such as age, gender, and polypharmacy, should also be taken into consideration. Please get in touch with the viral hepatitis team if further guidance is required or the immunosuppressive therapy is not listed in the tables below.

Table 3. Risk of reactivation with immunosuppressive agents in HBsAg positive patients[1-6]		
Risk of reactivation	**Immunosuppressive therapy**	**Prophylaxis**
High risk >10%	Alkylating agents e.g. cyclophosphamide, ifosfamide, melphalan Anthracyclines including doxorubicin, epirubicin B-cell depleting agents including rituximab, ocrelizumab, epratuzumab, ofatumumab, alemtuzumab, ibritumomab Bone marrow transplant, haemopoietic stem cell transplant or solid organ transplant Calcineurin inhibitors e.g. ciclosporin, voclisporin, tacrolimus CAR-T cell immunotherapy High-dose corticosteroids (equivalent to prednisolone>20mg OD for >4weeks OR >40mg OD any duration) High risk cytokine modulators: ustekinumab and Janus kinase (JAK) inhibitors including; baricitinib, filgotinib, tofacitinib, upadacitinib Direct-acting antivirals for Hepatitis C Immune checkpoint inhibitors including PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors and LAG-3 inhibitors e.g. nivolumab, pembrolizumab, cemiplimab, impilimumab, atezolizumab, avelumab, durvalumab, relatlimab Immunomodulatory drugs (IMiDs) such as lenolidamide, pomalidomide, thalidomide Local therapy for HCC including TACE mTOR inhibitors e.g. everolimus More potent TNF-α inhibitors including infliximab, adalimumab, certolizumab, golimumab Tocilizumab Tyrosine-kinase inhibitors including imatinib, nilotinib, sunitinib	Anti-viral prophylaxis

Moderate risk (1%-10%)	Avacopan Systemic chemotherapy Cladribine Moderate-dose corticosteroids (equivalent to prednisolone 10mg OD for >4 weeks) Moderate risk cytokine modulators: abatacept, bimekizumab, guselkumab, ixekizumab, mirikizumab, mogamulizumab, natalizumab, Risankizumab, sarilumab, secukinumab, vedolizumab, alemtuzumab Histone deacetylase inhibitors (HDIs) such as romidepsin Proteasome inhibitors such as bortezomib Less potent TNF-α inhibitors including etanercept	Anti-viral prophylaxis
Low risk (<1%)	Antimetabolites including; azathioprine, 6-mercaptopurine, methotrexate Apremilast Short-term low dose corticosteroids equivalent to prednisolone <10mg OD Intra-articular steroid injections (extremely low risk) Leflunomide Mycophenolate S1P receptor modulators e.g. fingolimod, ozanimod, ponesimod, siponimod Sulfasalazine	Anti-viral prophylaxis

Table 4: Risk of reactivation with immunosuppressive agents in HBsAg negative patients, HBcAB positive patients[1-6]		
Risk of reactivation	**Immunosuppressive therapy**	**Prophylaxis**
High risk	B-cell depleting agents including: rituximab, ocrelizumab, epratuzumab, ofatumumab, alemtuzumab, ibritumomab Bone marrow transplant, haemopoietic stem cell transplant or solid organ transplant Immunomodulatory drugs (IMiDs) such as lenolidamide, pomalidomide, thalidomide JAK inhibitors including: baricitinib, filgotinib, tofacitinib, upadacitinib	Anti-viral prophylaxis
Moderate risk	Alkylating agents e.g. cyclophosphamide, ifosfamide, melphalan Anthracyclines including doxorubicin, epirubicin Avacopan Calcineurin inhibitors e.g. ciclosporin, voclisporin and tacrolimus CAR-T cell immunotherapy Systemic chemotherapy Cladribine Moderate and high-dose corticosteroids (equivalent to prednisolone>10mg OD for >4weeks) Cytokine modulators: abatacept, anakinra, bimekizumab, daratumumab, guselkumab, ixekizumab, mirikizumab, mogamulizumab, natalizumab, Risankizumab, sarilumab, secukinumab, tocilizumab, ustekinumab, vedolizumab Direct-acting antivirals for Hepatitis C Histone deacetylase inhibitors (HDIs) such as romidepsin Integrin inhibitors Local therapy for HCC including TACE Proteasome inhibitors such as bortezomib TNF-α inhibitors including: infliximab, adalimumab, certolizumab, etanercept, golimumab Tyrosine-kinase inhibitors including imatinib, nilotinib, sunitinib	Monitor*

Low risk	Antimetabolites including: azathioprine, 6-mercaptopurine, methotrexate Apremilast Low dose corticosteroids (equivalent to 10mg prednisolone OD for > 4 weeks or intra-articular steroid injections) Any dose of corticosteroids daily for < 1 week Leflunomide Mycophenolate S1P receptor modulators e.g. fingolimod, ozanimod, ponesimod, siponimod Sulfasalazine	No anti-viral prophylaxis Monitor
Unknown risk	Belimumab Immune checkpoint inhibitors such as anti-PD-L1 (e.g. nivolumab), anti-PD-1 (e.g. pembrolizumab) and anti-CTLA4 (e.g. ipilimumab). mTOR inhibitors (e.g. everolimus)	Anti-viral prophylaxis To prevent potential interruption of treatment
* If unable to monitor reliably every 3 months, then consider anti-viral prophylaxis. Consider the cumulative effect of immunosuppressive therapies.		

Treatment recommendations and prescribing information

Patients requiring antiviral prophylaxis should be referred to the viral hepatitis team for prescribing and follow up. If patient care is impacted by increased burden of appointments, please consider taking over the prescribing of antiviral therapy. The antiviral team are happy to be involved for support and guidance.

Entecavir should be used as the first line anti-viral agent. Tenofovir may be used in the case of intolerance or if the patient is of child-bearing potential as tenofovir is the only antiviral of choice in pregnancy. In instances of pregnancy, please contact the Viral Hepatology Team. Please see table 5 for dose adjustments in renal impairment.

Entecavir and tenofovir are hospital-only medications and must be prescribed on a hospital outpatient prescription, not an FP10 prescription. Where possible, start antiviral prophylaxis 2 weeks before commencing the immune-suppressing agent.

Table 5. Antiviral dosing in renal impairment

eGFR	Entecavir	Tenofovir disoproxil (TDF)
≥50 mL/min	0.5 mg OD	245 mg OD
30–49 mL/min	0.5 mg on alternate days / 0.3 mg OD	245 mg on alternate days
10–29 mL/min	0.5 mg twice per week	245 mg twice per week
<10 mL/min	0.5 mg once weekly	No recommendation
Haemodialysis	0.5 mg once weekly given after haemodialysis	245 mg once weekly given after haemodialysis

Clinical monitoring

For those not on anti-viral prophylaxis

For HBsAg negative low-risk patients not on anti-viral prophylaxis, check ALT, HBsAg and HBV DNA **every 3 months** while on immunosuppressive therapy and **for 12 months after** cessation of the immunosuppressant to assess for HBV reactivation.[7,8]

For those prescribed anti-viral prophylaxis

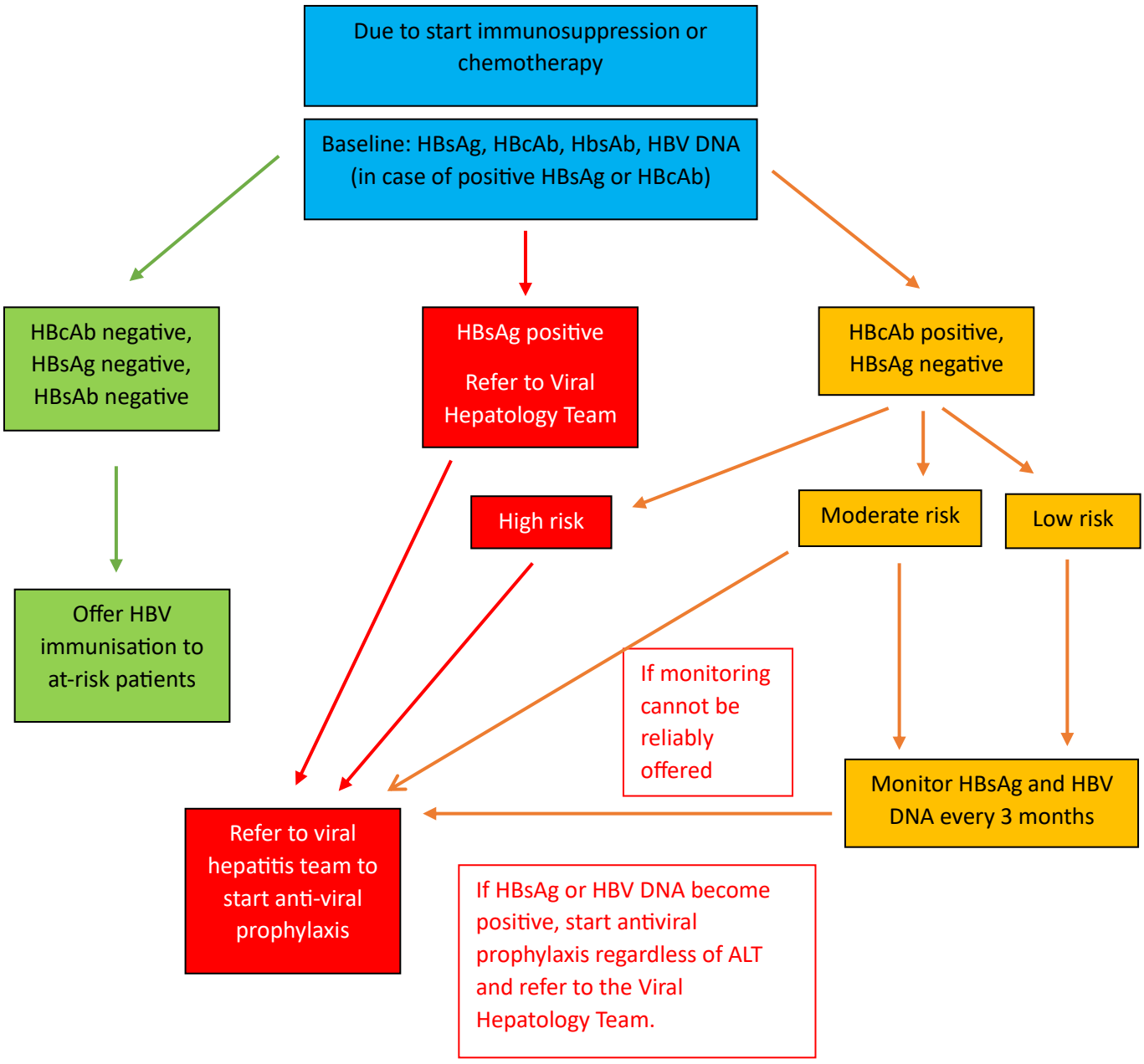
Specialist teams should monitor liver function and hepatitis markers **3 months after initiation of antiviral prophylaxis and 6 monthly thereafter.** This should include ALT, biochemistry, HBsAg, HBV DNA (viral load). Antiviral prophylaxis should continue for 12 months after withdrawal of the immunosuppressive agent, and blood monitoring should occur for **12 months after the antiviral has been stopped.**

Reactivation

The following criteria are reasonable for HBV reactivation: (1) HBV DNA is detectable or (2) reverse HBsAg seroconversion occurs (reappearance of HBsAg). A hepatitis flare is reasonably defined as an ALT increase to ≥3 times the baseline level and >100 U/L.[8]

If there is reactivation of hepatitis B, an urgent referral should be made to the viral hepatitis service. Patients with AST/ALT >100 should have their HBV DNA (viral load) repeated urgently and discuss with the hepatology service. Please contact the on-call general hepatology team for urgent clinical advice if deterioration of liver function tests occur that are unrelated to hepatitis B reactivation.

Appendix 1: Guidance on how to manage patients starting immunosuppressive therapy[1]



Contact information

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(Adapted from King's College Hospital Guidelines with permission).
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