Management of Hepatitis B

Background
HBV is contracted either sexually or by blood to blood transmission. The combined prevalence of HBV and HCV is just over 2% in the UK. More than 95% of immune competent patients clear HBV (loss of HBsAg with development of anti-HBs and anti-HBc), unless the disease is contracted in childhood, when 10% or less clear HBV. The patients who do not clear the virus develop a protracted relapsing/remitting chronic hepatitis. Untreated, up to 15% of adults with chronic HBV (CHB) develop cirrhosis and of those up to 1/3 develop HCC or decompensated cirrhosis; up to 25% of children with CHB eventually become cirrhotic and up to 20% of those develop HCC or decompensated cirrhosis.

Who to test
We recommend that the following groups are tested for hepatitis B infection:
- Pregnant women
- Infants born to HBsAg-positive mothers
- Household contacts and sexual partners of HBV-infected individuals
- Individuals who are the source of blood or body fluid exposures
- Individuals infected with HIV
- Individuals born in geographic regions with high HBsAg prevalence (≥2%)
- UK born Individuals not vaccinated as infants whose parents were born in geographic regions with a significant HBsAg prevalence
- Intravenous drug users
- Men who have sex with men
- Individuals with elevated ALT/AST of unknown aetiology
- Individuals with selected medical conditions who require immunosuppressive therapy

How to test and interpretation/management of results

Screening. A serum sample should be sent. A guide to interpretation and management of results follows.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>Interpretation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg anti-HBc</td>
<td>Negative</td>
<td>Susceptible</td>
<td>Vaccination recommended if at risk of infection</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Immune due to natural infection</td>
<td>Should seek advice if immunosuppressed in the future. No other action is required.</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg anti-HBc</td>
<td>Negative</td>
<td>Immune due to hepatitis B vaccination</td>
<td>Successful vaccination. No further action required.</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**HBsAg**  
**anti-HBc IgM**  
**anti-HBc**  
**anti-HBs**

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Positive</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acutely infected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>See management below.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronically infected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full workup* and referral to hepatology in one of the hepatitis B treatment centres.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Positive</th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interpretation unclear; four possibilities:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Resolved infection (most common)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. False-positive anti-HBc, thus susceptible</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. “Low level” chronic infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Resolving acute infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat tests to include LFT and HBV DNA. If LFT normal and HBV DNA negative, vaccinate if susceptible. Otherwise for full workup and referral to hepatology in one of the hepatitis B treatment centres.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Workup for patients with evidence of chronic HBV infection.* A full liver screen, HCV genotyping, HIV testing, HAV immunity assessment and an ultrasound scan to stage liver disease should be undertaken preferably before referral to secondary care. The liver screen includes: hepatitis B DNA level, liver autoantibodies, immunoglobulin profile, alpha-1 antitrypsin level, caeruloplasmin (if < 50 y o), ferritin, HBA1c, random glucose, LFT, AST, INR, UE and FBC.

**Hepatitis B treatment centres**

Usually, patients should be referred to their nearest treatment centre. These are:

- Addenbrooke’s Hospital
- Basildon Hospital
- Bedford Hospital
- Broomfield Hospital
- Ipswich Hospital
- King’s Lynn Hospital
- Luton and Dunstable Hospital
- Norfolk and Norwich Hospital
- Peterborough Hospital
- Southend Hospital
- West Suffolk Hospital

**Acute hepatitis B infection**

The serological profile of acute HBV infection is given above. Incubation period is 1 to 4 months to symptoms. Patients are infectious from several weeks before symptoms until clearance of the virus. Anti-core IgM develops around the time of symptoms, HBsAg and HBV DNA several weeks before symptoms.

Acute HBV leads to jaundice in about 30% of adults. Overall 95% adults will clear the virus and have long term immunity, 5% will develop chronic hepatitis (with 15% developing cirrhosis and 5% developing liver cancer or failure in the future) and < 0.5% will develop acute liver failure.

Management of acute HBV is supportive. Jaundice and transaminitis can be managed as an outpatient. Liver impairment (elevated PT) as an inpatient, until the course of the infection is ascertained. It is reasonable to treat patients with liver impairment with tenofovir or entecavir, although there are no robust data to supporting this recommendation.
HBsAg loss occurs within six months in the majority of patients. Persistence beyond this usually indicates chronic infection. If therapy is given for acute HBV, this can be stopped on loss of HBsAg.

Management of chronic hepatitis B infection

Patients with CHB go through the following disease phases. The combination of ALT, HBV DNA and serological profile characterizes which phase a patient is in. This guides management.

Hepatitis B phases

Immune tolerance (phase 1). Conceptually, viral replication is undetected by the immune system. Patients are highly infectious, but do not develop liver damage. This usually lasts until the age of between 20 and 40 for childhood CHB, but is not usually prolonged for adults who develop CHB.

Immune reactive/immune clearance (phase 2). During this phase, which lasts for between several weeks and several years, the immune system becomes active as detected by the development of anti-HBe. Significant liver damage may occur and close monitoring of patients with immune tolerant disease should occur by means of 3 monthly ALT and 6 monthly HBV DNA levels to detect entry into the immune reactive phase. An increased ALT or HBV DNA > 2000 IU/ml usually indicates liver biopsy with liver damage necessitating treatment.

Low replication/inactive carrier state (phase 3/4). This is sometimes referred to as low risk CHB. However, immune escape may occur in this phase and at least six monthly ALT and HBV DNA assessments should be made with flares of either necessitating further assessment by means of a biopsy. Interval elastography may be useful in monitoring for development of fibrosis in this phase, with an elevated score being investigated with liver biopsy. This approach allows the detection of eAg negative CHB that often requires treatment.

HBsAg negative phase (phase 5). This is characterised by development of anti-HBsAg and loss of HBsAg. The disease has ‘burnt out’.

These phases are demonstrated graphically below in a graph taken from the HBV NICE guidelines.

Common clinical issues

When to treat and choice of treatment. Treatment will be preceded by liver biopsy and/or Fibroscan. With significant inflammation or fibrosis, treatment should be instigated. Whilst pegylated IFN can be offered to all patients in accordance to NICE guidelines, it is often reserved for eAg positive patients with positive prognostic features for clearance of eAg:
• High ALT
• Significant interface hepatitis
• Female gender
• Low HBV DNA levels

Dynamics of HBV DNA and HBsAg response to interferon are important in defining outcome of pegylated IFN treatment. After 24 weeks of therapy, if HBV DNA level has decreased by less than 2 log\textsuperscript{10} IU/ml and/or if HBsAg is greater than 20,000 IU/ml then treatment should be stopped and oral antiviral therapy considered. Otherwise, it should continue for 48 weeks with monitoring of ALT, eAg/sAg status and HBV DNA thereafter. Persistent hepatitis at this stage necessitates oral antiviral therapy.

Oral antiviral agents. Current first line is entecavir 0.5 mg/1 mg (dose dependent on clinical scenario and eGFR) or tenofovir 245 mg daily (dose depending on eGFR). Once the decision to instigate oral therapy is made, patients should be counselled concerning side effects (usually asymptomatic, but the more common ones are GI disturbance and musculoskeletal pain; worrying ones are renal failure, lactic acidosis and pancreatitis). Kidney tests should be taken pre-treatment and at two weeks. Follow up at 4 weeks (UE) then 3 monthly UE and LFT thereafter with HBV DNA levels until suppression has been achieved with HBV DNA 6 monthly thereafter. Second line therapy or therapy for patients with decompensated liver disease should be with entecavir. Treatment should be considered long term/life long in most cases.

Failure to suppress HBV DNA should prompt mutational analysis, but resistance is rare/not described and so compliance should be investigated in this context.

Renal impairment on antiviral therapy. Development of renal impairment on tenofovir or adefovir should be investigated by a renal screen (blood tests [ANA, dsDNA, complement, ANCA, anti-GBM, paraprotein], urine dip and a renal ultrasound scan). If that is negative and a dose reduction is necessary (i.e. eGFR < 50), then an alternative agent such as entecavir or cessation of therapy should be considered. If the renal function fails to improve with this strategy then a referral to nephrology should be made.

Decision to biopsy. It is reasonable to have a low threshold for liver biopsy for patients with CHB. If the ALT is elevated > 2X normal in the presumed immune tolerant state, or the ALT is elevated > 2X normal and/or HBV DNA > 2000 IU/ml in the eAg neg state and the patient has not been biopsied before, then a biopsy should be considered to ascertain whether there is significant liver disease requiring treatment. All biopsies should be discussed. Any equivocal indications for biopsy should also be discussed. In practice, an ALT above the normal range would be argued by some to be > 2X upper limit of normal.

Use of elastography. Liver biopsy gives information regarding grade and stage of liver disease whereas elastography informs stage only. Elastography is often useful at initial assessment. Additionally, it may be useful when information regarding stage alone is required. Examples include follow up of patients with bland biopsies but continually abnormal ALT or high viral load. NICE guidelines recommend annual elastography for patients with eAg negative disease, which may be excessive. Interval elastography every few years is probably useful in this group.

Follow up interval guide. Immune tolerant disease (phase 1): 3 monthly blood tests (LFT most important) and 6 monthly clinic/blood test visits. Immune clearance/reactive disease (phase 2) will depend on management strategy. Low replication/inactive carrier state (phase 3/4): 3 monthly blood tests (LFT and HBV DNA) and 6 monthly clinic/blood test visits for one year. 6 monthly blood tests and annual clinic/blood test visits unless HCC surveillance is required. HBsAg/anti-HBs every two years. Patients on oral anti-viral therapy: 3-6 monthly clinic/blood test (LFT, UE, HBV DNA 6 monthly when established)/prescription visits.

HCC surveillance. This should be offered to cirrhotic patients, male patients > 40 yrs and female patients > 50 yrs with childhood acquisition of CHB, and patients with CHB and a family history of HCC. Surveillance should be by six monthly ultrasound and AFP measurements.

Immunization. Patients with CHB who contract HAV are at risk of following a fulminant course. Vaccination of anti-HAV IgG negative patients should therefore be undertaken.

Contact tracing/disease prevention. When patients are first seen, a recommendation should be made for screening of current/previous sexual and blood contacts. Those at risk of exposure from the patient (partners and children usually) should be screened and immunization recommended. Barrier methods of contraception should be used until immunization. The “Green Book” is available online and gives detailed advice regarding vaccination schedules.

Hepatitis B vaccination schedules. The standard course of immunisation for adults is three injections at 0, 1 and 6 months. An accelerated course of 0, 1 and 2 months is possible - also for combined hepatitis A and B vaccines. Adults who need protection very quickly (eg within 48 hours of exposure) can have a schedule of 0, 7 and 21 days. After an accelerated course, a booster at one year is recommended. A
booster is recommended at 5 years if continued exposure is likely. Anti-HBsAg titres are recommended for assessment of vaccination efficacy for healthcare workers and patients with renal failure.

Universal vaccination is now available as per the schedule below. For those born to HBsAg positive mothers, additional vaccination at 0 and 4 weeks is required with a hepatitis B screen at 12 months. Additional HBlg is given to those born to eAg positive patients or those with an HBV DNA > 10^6 IU/mL at any time during pregnancy. A booster vaccination is no longer recommended pre-school.

*Newborn infants born to a hepatitis B negative woman but known to being home to a household with another hepatitis B infected person may be at immediate risk of hepatitis B infection. In these situations, a monovalent dose of hepatitis B vaccine should be offered before discharge from hospital. They should then continue on the routine childhood schedule commencing at eight weeks.

Hepatitis B doses in the immunisation schedule for routine childhood and selective neonatal hepatitis B programmes – taken from Public Health England guidance

<table>
<thead>
<tr>
<th>Age</th>
<th>Routine childhood programme</th>
<th>Babies born to hepatitis B infected mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>√</td>
<td>Monovalent HepB (Engerix B® or HBvaxPRO Paediatric®) (with HBIG if indicated)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>√</td>
<td>Monovalent HepB (Engerix B® or HBvaxPRO Paediatric®)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>DTaP/IPV/Hib/HepB (Infanrix hexa®)</td>
<td>DTaP/IPV/Hib/HepB (Infanrix hexa®)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>DTaP/IPV/Hib/HepB (Infanrix hexa®)</td>
<td>DTaP/IPV/Hib/HepB (Infanrix hexa®)</td>
</tr>
<tr>
<td>16 weeks</td>
<td>DTaP/IPV/Hib/HepB (Infanrix hexa®)</td>
<td>DTaP/IPV/Hib/HepB (Infanrix hexa®)</td>
</tr>
<tr>
<td>1 year</td>
<td>√</td>
<td>Monovalent HepB (Engerix B® or HBvaxPRO Paediatric®) Test for HBsAg</td>
</tr>
</tbody>
</table>

Pregnancy. Interferon therapy is contra-indicated with pregnancy. If a patient's liver disease is significant enough to require oral anti-viral agents then they should be prescribed as the benefits outweigh the risks. No cases of teratogenicity secondary to tenofovir beyond background risk have been reported. Significant liver disease is associated with miscarriage. Suppressing HBV DNA reduces the risk of vertical transmission. Indeed, pregnant women with CHB and an HBV DNA > 10^6 IU/ml carry a vertical transmission risk of about 10% despite passive and active vaccination of newborn infants and should therefore discuss viral DNA suppression pre-delivery. Tenofovir is a reasonable choice for this and should be started early in the third trimester and continued until 3/12 after delivery with careful monitoring of ALT thereafter to detect any rebound hepatitis. See immunization of newborns above. Breastfeeding is safe.

Immune suppression. HBsAg positive patients should have HBV DNA suppressed before receiving immunosuppressive therapy or chemotherapy. HbsAg neg, antiHBc pos patients should have an HBV DNA performed and if this is positive they should be treated. If HBV DNA is negative in this context then 3-monthly monitoring of ALT and HBV DNA should be performed and treatment instigated if HBV DNA becomes positive. The exception to this is when rituximab and/or combined regimens for haematological malignancies are used in which case oral anti-virals should be considered. This includes patients after bone marrow/stem cell transplantation. Entecavir or tenofovir are reasonable choices in all of these contexts and should be given until 12 months after cessation of immune suppression. Pre-emptive vaccination for HBV is recommended pre-immune suppression for those who have not been exposed to HBV.
Healthcare workers. Brief guidelines for vaccination of non-infected healthcare workers and healthcare workers with CHB are given above. Detailed guidance regarding patients chronically infected with HBV are given here. HBeAg positive healthcare professionals and those with a viral load > 20000 IU/mL at presentation cannot perform exposure prone procedures (EPPs). HBeAg negative individuals with HBV DNA < 200 IU/mL can perform EPPs and require annual testing. Those HBeAg negative individuals with HBV DNA 200 IU/mL to 20000 IU/mL can perform EPPs if HBV DNA is persistently suppressed at 12 weekly review by anti-viral agents to < 200 IU/mL. Management of such cases should be driven by occupational health.

cAb positive donor organs. For cAb positive liver donation, recipients should receive antiviral prophylaxis for at least one year after transplantation with 3 monthly monitoring of HBV DNA. At one year, prophylaxis could be stopped for sAb pos recipients with monitoring of HBV DNA thereafter (months 1, 3, 6, 9, 12 then at clinic visits). Otherwise, it should be continued long term. For cAb positive non-liver organ donation, cAb neg, sAb neg recipients should receive antiviral prophylaxis for at least one year with three monthly monitoring of HBV DNA. At one year, prophylaxis could be stopped with monitoring of HBV DNA thereafter (months 1, 3, 6, 9, 12 then at each clinic visits). Other recipients should have 3 monthly monitoring of HBV DNA with treatment if they become positive. An appropriate choice of antiviral is tenofovir - dosed according to renal function.

HIV/HBV co-infection

Staging and surveillance guidelines are as for chronic infection. The current recommendation from BHIVA is to treat any patient with HIV viraemia. Regimen choice should include an agent which also suppresses HBV (usually tenofovir) and HBV viraemia monitored during therapy.

HBV/HCV co-infection

Initial management is by assessing which disease is dominant. This should be treated first. If HCV is treated before HBV then HBV activity should be closely monitored, as flares of hepatitis may occur once the suppressive activity of HCV is released.

Monitoring of patients on hepatitis B oral antiviral therapy

Baseline: LFT, HBV DNA, renal function, bone profile, vitamin D, urine dip and FRAX score

Every clinic visit: Clinical assessment, LFT, HBV DNA and renal function; bone profile if on tenofovir or adefovir

Annually for those on tenofovir and adefovir: urine dip, vitamin D level and FRAX score

Renal impairment

Development of renal impairment on tenofovir or adefovir should be investigated by a renal screen:

- blood tests [ANA, dsDNA, complement, ANCA, anti-GBM, paraprotein],
- urine dip with protein: creatinine and albumin: creatinine if positive
- urine BJP
- renal ultrasound scan

If that is negative and a dose reduction is necessary (i.e. eGFR < 50), then an alternative agent such as entecavir or cessation of therapy should be considered.

If the renal function fails to improve with this strategy then a referral to nephrology should be made.
Dosing recommendations in renal impairment:

<table>
<thead>
<tr>
<th>Renal function</th>
<th>Tenofovir</th>
<th>Entecavir</th>
<th>Adefovir</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &gt;50 ml/min</td>
<td>245 mg daily</td>
<td>0.5-1 mg daily</td>
<td>10 mg daily</td>
<td>100 mg daily</td>
</tr>
<tr>
<td>eGFR 30 - 50 ml/min</td>
<td>245 mg every 2 days</td>
<td>0.5 mg daily</td>
<td>10 mg every 2 days</td>
<td>50 mg daily</td>
</tr>
<tr>
<td>eGFR 10 - 30 ml/min</td>
<td>245 mg every 3 days</td>
<td>0.5 mg every 2 days</td>
<td>10 mg every 3 days</td>
<td>25 mg daily</td>
</tr>
<tr>
<td>eGFR &lt; 10 ml/min</td>
<td>245 mg weekly</td>
<td>0.5 mg every 3 days</td>
<td>10 mg every 3 days</td>
<td>15 mg daily</td>
</tr>
<tr>
<td>RRT (give after RRT session)</td>
<td>245 mg weekly</td>
<td>0.5 mg every 3 days</td>
<td>10 mg every 3 days</td>
<td>10 mg daily (suspension required for lower doses)</td>
</tr>
</tbody>
</table>

**Proteinuria**

*Trace* with normal renal function then repeat at next clinic visit with an assessment of blood pressure and other relevant co-morbidities/medications.

*Recurrent trace or 1+/2+* then assess BP, relevant co-morbidities/medications and manage as per renal impairment.

If proteinuria does not resolve on regimen change then referral to renal team is recommended.

**Hypophosphatemia**

For all cases, the investigations below should be performed. In terms of treatment:

- > 0.5 mmol/L: monitor
- 0.3 – 0.5 mmol/L: treat with oral supplementation, monitor closely;
- < 0.3 mmol/L: admit for supplementation, investigation and management.

Assess for other causes: dietary, chronic diarrhea, respiratory alkalosis, musculoskeletal symptoms, high alcohol intake, other drug causes, PTH, vitamin D, Mg, bicarbonate and renal function. If all normal, consider switch in antiviral regimen.

**Elevated FRAX score**

Investigate with DEXA scan.

If osteopenia: vitamin D/calcium supplements and consider switch from tenofovir.

If osteoporotic: to commence bisphosphonate and consider switch from tenofovir.