TAYSIDE SEXUAL HEALTH & BLOOD BORNE VIRUS MANAGED CARE NETWORK

Hepatitis B (HBV)
Clinical Guidelines

October 2013
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BBV MCN: Guidelines for the management of Hepatitis B

SECTION 1: AIMS

Remit of the Guidelines

This guideline provides evidence-based recommendations covering all stages of the patient care pathway; screening, testing, diagnosis, referral, treatment, care and follow up of patients with, or exposed to Hepatitis B Virus (HBV) infection.

Aims of Management Guidelines

- To improve communication between health care professionals caring for clients/patients with HBV
- To standardise services provided in primary and secondary care
- To identify patients suitable for treatment
- To monitor the progress of clients/patients diagnosed with HBV

Background

Hepatitis B is a viral disease process caused by the hepatitis B virus (HBV). The virus is endemic throughout the world. When transmission occurs vertically (from mother to child) or horizontally in small children the infection nearly always becomes chronic. By contrast, when transmission occurs in adolescents/adults usually via sexual contact, or contaminated needles the infection usually resolves unless the individual is immunocompromised.

Individuals chronically infected with HBV are at increased risk of developing cirrhosis, leading to hepatic decompensation and hepatocellular carcinoma (HCC). Although many patients with chronic HBV infection do not develop hepatic complications, there is a potential for serious illness to develop during their lifetime, and it is more likely to occur in men.

Hepatitis B vaccination is highly effective, and in some countries universal vaccination at a young age is desirable. At the very least, vaccination should be offered to all individuals who are at risk. Pregnant women must be screened for hepatitis B before delivery, as this offers an opportunity to prevent another generation of chronically infected persons.

SECTION 2: PREVENTION OF HEPATITIS B

2.1: Introduction

Type B hepatitis is caused by the hepatitis B virus (HBV), a small enveloped DNA virus that infects the liver causing hepatocellular necrosis and inflammation. HBV can cause either an acute illness or chronic, persistent infection. Acute or chronic infection can lead to severe liver damage and is therefore potentially fatal.

2.2: Prevalence

- Two billion people worldwide have been infected with the virus and about 350 million live with chronic infection.
- The prevalence of infection varies worldwide .High endemic areas (>8%) include sub Saharan Africa most of Asia and the Pacific islands whereas most of western Europe and North America are low endemic areas (<2%)

UK statistics

- Low prevalence but varies across country, higher in those born in high-endemicity countries.
- Prevalence rates in antenatal women are around 0.14% but rises to 1% in certain inner city areas.
- Laboratory reports of acute HBV are between 600-800 cases per year.

2.3: Transmission

The virus is transmitted by parenteral exposure to infected blood or body fluids. Transmission mostly occurs:

- through vaginal or anal intercourse
- as a result of blood-to-blood contact (e.g. sharing of needles and other equipment by injecting drug users (IDUs), 'needlestick' injuries)
- through perinatal transmission from mother to child.

Lower risk of transmission can occur

- in household contacts if they share toothbrushes or razor blades.
- following bites from infected persons, although this is rare.

Transfusion-associated infection is now rare in the UK as blood donations are screened. Viral inactivation of blood products has eliminated these as a source of infection in this country.

2.4: Primary Prevention

Hepatitis B vaccine

- Hepatitis B vaccine is an inactivated vaccine produced using recombinant DNA technology.
- A combined vaccine is also available where protection against both hepatitis A and hepatitis B infections is required.
- Around 10 to 15% of adults fail to respond to three doses of vaccine or respond poorly.
- Poor response associated with age over 40 years, obesity, smoking, alcoholics, immunosuppressed patients and those on renal dialysis.

Hepatitis B Immunoglobulin

- Specific hepatitis B immunoglobulin (HBIG) provides passive immunity and can give immediate but temporary protection after accidental inoculation or contamination with hepatitis B-infected blood. HBIG is given concurrently with hepatitis B vaccine and does not affect the development of active immunity.
- The use of HBIG in addition to vaccine is recommended only in high-risk situations or in a known non-responder to vaccine. Whenever immediate protection is required, immunisation with the vaccine should be given.
- HBIG should be given as soon as possible, ideally within 48 hours, although it should still be considered up to a week after exposure.

Pre-exposure Immunisation

The objective is to provide a minimum of three doses of hepatitis B vaccine for individuals at high risk of exposure to the virus because of their lifestyle, occupation or other factors.
Where testing for markers of current or past infection is clinically indicated, this should be done at the same time as the administration of the first dose. Vaccination should not be delayed while waiting for results of the tests.

Pre-exposure immunisation is recommended for the following groups

- Injecting drug users
- Individuals who change sexual partners frequently
- Close family contacts of a case or individual with chronic hepatitis B infection
- Families adopting children from countries with a high or immediate prevalence of hepatitis B
- Foster carers
- Individuals receiving regular blood or blood products and their carers
- Patients with chronic kidney disease
- Patients with chronic liver failure
- Inmates of custodial institutions
- Individuals in residential accommodation for those with learning difficulties
- People travelling to or going to reside in areas of high or intermediate prevalence

- Individuals at occupational risk such as healthcare workers in UK and overseas , laboratory staff, staff of residential and other accommodation for those with learning needs, morticians and embalmers, prison staff

Post-exposure Immunisation

Post-exposure prophylaxis is recommended for the following groups.

1. Sexual contacts of individuals suffering from acute hepatitis B, and who are seen within one week of last contact, should be offered protection with HBIG and vaccine. Sexual contacts of an individual with newly diagnosed chronic hepatitis B should be offered vaccine; HBIG may be added if unprotected sexual contact occurred in the past week.

2. Persons who are accidentally inoculated or contaminated .This includes those who contaminate their eyes or mouth, or fresh cuts or abrasions of the skin, with blood from a known hepatitis B surface antigen (HBsAg) positive person.

3. Babies born to mothers who are chronically infected with HBV or to mothers who have had acute hepatitis B during pregnancy

    - All pregnant women should be offered screening for hepatitis B infection during each pregnancy. Confirmatory testing and testing for hepatitis B e-markers of those mothers shown to be infected should follow.
    - Where an unbooked mother presents in labour, an urgent HBsAg test should be performed to ensure that vaccine can be given to babies born to positive mothers within 24 hours of birth.
    - Babies born to highly infectious mothers should receive HBIG as well as active immunisation (see Table 1)

Hepatitis B status of mother	Baby should receive Hepatitis B vaccine	Baby should receive HBIG
Mother is HbsAg positive and HbeAg positive	Yes	Yes
Mother is HbsAg positive HbeAg negative and anti-Hbe negative	Yes	Yes
Mother is HbsAg positive where e-markers have not been determined	Yes	Yes
Mother had acute hepatitis B during pregnancy	Yes	Yes
Mother is HbsAg positive and anti-HBe positive	Yes	No
A woman who is HbsAg seropositive and known to have an HBV DNA level equal or above 1x10x6IU/ml in an antenatal sample	Yes	Yes

Table 1: Immunisation of babies born to mothers with hepatitis B

Abbreviations

- HbsAg – Hepatitis B surface antigen
- HbeAg – Hepatitis B e antigen
- Anti-Hbe – e antibody

- The response to hepatitis B vaccine is lower in pre-term, low-birth weight babies. It is, therefore, important that premature infants receive the full paediatric dose of hepatitis B vaccine on schedule.
- Babies with a birthweight of 1500g or less, born to mothers infected with hepatitis B, should receive HBIG in addition to the vaccine, regardless of the e-antigen status of the mother.

- For post-exposure prophylaxis in babies born to mothers infected with hepatitis B, the accelerated immunisation schedule is preferred. For these babies this will mean an initial dose of vaccine at birth, with further doses at one and two months of age and a fourth dose at one year of age.
- Testing for HBsAg at one year of age will identify any babies for whom this intervention has not been successful and who have become chronically infected with hepatitis B, and will allow them to be referred for assessment and any further management. This testing can be carried out at the same time as the fourth dose is given.

2.5: Primary immunisation

Pre-exposure prophylaxis

- An accelerated schedule should be used in most adult and childhood risk groups, with vaccine given at zero, one and two months. For those who are at continued risk, a fourth dose is recommended at 12 months.
- An alternative schedule at zero, one and six months should only be used where rapid protection is not required and there is a high likelihood of compliance.
- Engerix B® can also be given at a very rapid schedule with three doses given at zero, seven and 21 days. When this schedule is used, a fourth dose is recommended 12 months after the first dose. This schedule is licensed for use in circumstances where adults over 18 years of age are at immediate risk such as persons travelling to areas of high endemicity, IDUs and prisoners.
- Twinrix Adult® vaccine can also be given at zero, seven and 21 days. This will provide more rapid protection against hepatitis B than other schedules but full protection against hepatitis A will be provided later than with vaccines containing a higher dose of hepatitis A. When this schedule is used, a fourth dose is recommended 12 months after the first dose.

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Post-exposure prophylaxis

An accelerated schedule of monovalent hepatitis B vaccine (or a combined vaccine of equivalent strength) should be used, with vaccine given at zero, one and two months. For those who are at continued risk, a fourth dose is recommended at 12 months. If HBIG is also indicated, it should be given as soon as possible, ideally at the same time as the first dose of vaccine.

Reinforcing immunisation

The full duration of protection afforded by hepatitis B vaccine has yet to be established. Levels of vaccine-induced antibody to hepatitis B decline over time, but there is evidence that immune memory can persist in those successfully immunised. However, recent evidence suggests that not all individuals may respond in this way. It is, therefore, recommended that individuals at continuing risk of infection should be offered a single booster dose of vaccine, once only, around five years after primary immunisation. Measurement of anti-HBs levels is not required either before or after this dose. Boosters are also recommended after exposure to the virus (as above).

2.6: Response to vaccine and the use of additional doses

Except in certain groups (see below), testing for anti-HBs is not recommended.

Those at risk of occupational exposure

- In those at risk of occupational exposure, antibody titres should be checked one to four months after the completion of a primary course of vaccine. It is preferable to achieve anti-HBs levels above 100mIU/ml, although levels of 10mIU/ml or more are generally accepted as enough to protect against infection.

- Responders with anti-HBs levels greater than or equal to 100mIU/ml do not require any further primary doses. In immunocompetent individuals, once a response has been established further assessment of antibody levels is not indicated. They should receive the reinforcing dose at five years as recommended above.

- Responders with anti-HBs levels of 10 to 100mIU/ml should receive one additional dose of vaccine at that time. In immunocompetent individuals, further assessment of antibody levels is not indicated. They should receive the reinforcing dose at five years as recommended above

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- An antibody level below 10mIU/ml is classified as a non-response to vaccine, and testing for markers of current or past infection is good clinical practice. In non-responders, a repeat course of vaccine is recommended, followed by retesting one to four months after the second course. Those who still have anti-HBs levels below 10mIU/ml, and who have no markers of current or past infection, will require HBIG for protection if exposed to the virus .

Patients with renal failure

- Due to the poor response to immunisation anti-HBs levels should be monitored annually and if they fall below 10mIU/ml, a booster dose of vaccine should be given to patients who have previously responded to the vaccine.

- Booster doses should also be offered to any haemodialysis patients who are intending to visit countries with a high endemicity of hepatitis B and who have previously responded to the vaccine, particularly if they are to receive haemodialysis and have not received a booster in the last 12 months

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SECTION 3: MANAGEMENT OF HEPATITIS B

3.1: Diagnosis of Acute Hepatitis B

The average incubation period is 60 to 90 days (range is 40 to 160 days). The disease generally lasts from one to six weeks but may be prolonged and can be fulminant. Acute hepatitis B resembles other forms of acute hepatitis clinically and cannot easily be distinguished by history, physical examination or routine serum biochemical tests.

Unusually, fulminant hepatitis B can occur during acute infection. This occurs in approximately 2 to 3% of cases. Fulminant hepatitis can lead to the rapid onset and development of acute hepatic failure with encephalopathy, coma and death.

Signs and symptoms of acute hepatitis B

- In the initial stages of HBV infection the symptoms are vague and ill-defined.
- The onset of hepatitis B is typically insidious, with non-specific symptoms of malaise, poor appetite and nausea, with pain in the right upper quadrant.
- Fever, when present, is usually mild.
- Roughly 30 to 50% of adult patients will develop jaundice. As jaundice sets in, the urine becomes darker and the stools paler.

3.2: Interpreting laboratory result

Various classifications of antibody indicate the stages of the immune response.

The three main HBV antigens are:

- HBsAg Hepatitis B surface antigen
- HBcAg Hepatitis B core antigen (HBcAg is not found in serum)
- HBeAg Hepatitis B e-antigen (denotes active viral replication)

HBcAg can stimulate IgM and IgG antibodies:

- immunoglobulin 'M' (IgM) indicating that HBV infection has occurred within the last six months
- immunoglobulin 'G' (IgG) indicating that HBV infection occurred more than six months earlier

The diagnosis of acute hepatitis B generally rests upon the finding of hepatitis B surface antigen (HBsAg) and IgM antibody to hepatitis B core (anti-HBc) in the serum of a patient with clinical and biochemical evidence of acute hepatitis.

- The first serological marker to be detectable in the serum is **HBsAg** which appears during the incubation period and rapidly rises in titre. In about 10% of patients HBsAg is cleared early and may not be detectable when the patient is first seen by the physician
- Concurrent with or shortly after the appearance of HBsAg in serum, **HBeAg** and **HBV DNA** are detectable. Disappearance of HBeAg, seroconversion to anti-HBe and a decline in HBV DNA indicates resolution of viral replication and predicts resolution of acute hepatitis B.
- In patients who develop chronic hepatitis B, HBeAg and HBV DNA usually remain high., however some patients with chronic infections may be negative for HBV DNA and / or HBeAg. **HBcAg** is not found in the serum
- The first antibody to arise during the course of typical acute hepatitis B is **anti-HBc. IgM anti-HBc** is positive in acute hepatitis B and is used to document the acute disease, rather than an exacerbation of disease.
- It generally persists for only a few months, making it a useful marker for the diagnosis of acute hepatitis B. **IgG anti-HBc**, indicative of chronic infection, generally persists for life. A proportion of patients with active chronic hepatitis B may also develop IgM anti-HBc, detected by sensitive tests.
- Core IgM sometimes is detectable at a low level in chronic infection
- Antibodies to HBsAg **(anti-HBs)** usually appear during convalescence following the surface antigen's disappearance. Anti-HBs alone is also a marker of immunisation.

3.3: Diagnosis of chronic hepatitis B

Chronic hepatitis B is defined as persistence of HBsAg in the circulation for more than six months.

The risk of developing chronic hepatitis B infection depends on the age at which infection is acquired. Chronic infection occurs in 90% of those infected perinatally but is less frequent in those infected as children (e.g. 20 to 50% in children between one and five years of age). About 5% or less of previously healthy people, infected as adults, become chronically infected. The risk is increased in those whose immunity is impaired.

Only a small percentage of patients with chronic infection give a history of acute hepatitis or jaundice. Physical examination in chronic hepatitis B may show no physical abnormalities and many patients show no symptoms of liver disease. If symptoms are present, they are usually non-specific and mild.

3.4: Phases of hepatitis B

Chronic hepatitis B is a dynamic process and the natural history can be divided into five phases which are not necessarily sequential.

Phase	Description
Immune tolerant phase:	HBeAg positive , high levels of serum HBV DNA , normal or low levels of aminotransferases , mild or no liver necroinflammation and slow or no progression to fibrosis,usually seen in those infected perinatally or in first years of life, patients highly contagious due to high levels of viraemia
Immune reactive phase:	HBeAg positive , lower levels of serum HBV DNA ,increased aminotransferases,moderate or severe liver necroinflammation,more rapid progression to fibrosis,more frequently reached in those infected in adulthood
Inactive HBV, carrier state	May follow seroconversion from HBeAg to anti-HBe antibodies,low or undetectable serum HBV DNA levels and normal aminotransferases favourable outcome with low risk of cirrhosis or HCC
HbeAg –negative CHB:	Variant forms of HBV (pre-core mutants) unable to secrete HBeAg are predominant, characterized by pattern of fluctuating levels of HBV DNA and aminotransferases and active hepatitis

3.5: Chronic Hepatitis B

The subsequent course of chronic hepatitis B is variable. Perhaps 15% to 20% of patients who acquire chronic infection in adulthood ultimately develop cirrhosis. Furthermore, the development of cirrhosis is usually slow, occurring over five to twenty years. Up to 9% may go on to develop HCC.

Infection in childhood may have a different prognosis. Typically, the infection is mild and associated with few symptoms and only minimal elevations of serum aminotransferases. The disease may change once adulthood is reached, with marked fluctuations in its activity and the development of cirrhosis in up to 40% of patients.

People with active inflammation and cirrhosis where there is a rapid cell turnover, are at increased risk of developing HCC. In endemic areas of HBV infection, HBV positive patients frequently have silent disease until the development of HCC. Ultrasound examinations and regular determinations of alpha fetoprotein can be used to screen for

HCC in high-risk populations and in individual patients, particularly those over the age of 40 who acquire HBV infection during childhood and who have cirrhosis.

3.6: Who should get tested?

HBV testing should be offered to anyone who has the following

- Has unexplained persistent abnormal liver function tests or unexplained jaundice
- Has ever injected drugs
- Babies born to chronically infected mothers at 12 months of age
- Individuals who change sexual partners frequently particularly MSM and male and female commercial sex workers
- Household contact with a person with chronic HBV
- Recipients of a blood transfusion in UK before 1991 or blood products before 1986
- Has been accidentally exposed to blood through a needlestick injury or violent injury
- Has had a tattoo piercings acupuncture or electrolysis where infection control is poor
- Has received medical or dental treatment in countries where infection control is poor
- Has come from a country with high endemicity
- All pregnant individuals

3.7: Information to be given on diagnosis

Patients should be informed about

- Methods of preventing transmission (for example, practising safe sex, cleaning up blood spills, not sharing razors or toothbrushes).
- Need to avoid alcohol.
- The importance of screening and vaccination being offered to sexual partners, other household members and children

SECTION 4: REFERRAL AND TREATMENT

4.1: Referral to specialist services

Patients with acute hepatitis B do not require referral to specialist service. Patients with chronic hepatitis B should be referred to specialist services in a timely fashion. Prior to referral current bloods should be available for LFTS, and hepatitis B DNA (Appendix 1)

4.2: Assessment within Specialist service (Appendix 1)

1.Blood tests

- HBV DNA detection and HBV DNA level measurement is essential for the diagnosis, decision to treat and subsequent monitoring of patients.
- Liver function tests
- Patients should be considered for treatment when HBV DNA levels are above 2000 IU/ml and/or the serum ALT levels are above the upper limit of normal (ULN) for the laboratory, and liver biopsy (or non-invasive markers when validated in HBV-infected patients) shows moderate to severe active necroinflammation and/or fibrosis using a standardised scoring system (for example at least grade A2 or stage F2 by METAVIR scoring)

2.. Investigations

- Abdominal Ultrasound
- Fibroscan
- Liver biopsy - A liver biopsy is helpful to ascertain the degree of necroinflammation and fibrosis.

4.3: Treatment for Hepatitis B

1.Treatment

Treatment is indicated for chronic disease. The goals are to prevent disease progression to cirrhosis and end stage liver disease, hepatocellular carcinoma and death. Treatment generally does not offer a cure, but it does help delay or prevent cirrhosis for people who respond. People who were born with the virus tend to respond less well, but treatment may still be recommended to help prevent cirrhosis developing and to reduce the chance of the infection being passed on.

Treatment decisions will be made by nursing and medical staff within Specialist service following EASL (1) and AASLD (2) guidelines.

(1) European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Management of chronic hepatitis B. Journal of Hepatology 2012 vol. 57 j 167–185
http://www.easl.eu/medias/cpg/issue8/English-Report.pdf

(2) American Association for the study of liver Disease (AASLD) Practice Guidelines Chronic Hepatitis B: Hepatology, Vol. 00, No. 00, 2015
https://www.aasld.org/sites/default/files/guideline_documents/hep28156.pdf

Current treatment options include

- Pegylated interferon.
- Anti-viral treatments
    - Current treatments include oral lamivudine entecavir, adefovir, tenofovir.
    - First line therapy for new patient's commencing on anti-virals will be Tenofovir or Entecavir if the patient had problems with renal function

2. Liver transplant

For some people with advanced cirrhosis, liver transplantation may be an option. Although this is a major operation, the outlook following a liver transplant can be very good. However, the new liver may also eventually become damaged by the persisting hepatitis B infection.

3: .Diet and alcohol

Most people with chronic hepatitis B will be advised to eat a normal healthy balanced diet. Ideally, anybody with inflammation of the liver should not drink alcohol. If you already have liver inflammation, alcohol increases the risk and speed of developing cirrhosis.

4.4: Follow up of patients in specialist service

Patients will be reviewed yearly in the specialist clinic (appendix 2), or 6 monthly in the following categories:

- Asian men over age of 40
- Asian women over age of 50
- All patients with cirrhosis
- Patients with family history of HCC
- Africans over age of 20
- HBV/HIV co-infection

Management of patients with cirrhosis

The patient will be individually assessed by a Hepatologist for consideration of treatment or hepatic transplantation.

If neither is deemed suitable or necessary, they will be placed on 6 monthly follow up, and on the hepatoma-screening programme which includes the measurement of alpha fetoprotein and ultrasound examination should take place at six monthly intervals

SECTION 4: REFERENCES AND PATIENT INFORMATION

References

Department of Health Immunisation against infectious disease - 'The Green Book'
http://www.dh.gov.uk/en/Publichealth/Healthprotection/Immunisation/Greenbook/DH_4097254

European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Management of chronic hepatitis B. Journal of Hepatology 2012 vol. 57 j 167–185
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https://www.aasld.org/sites/default/files/guideline_documents/hep28156.pdf

Patient information

British Liver Trust Hepatitis B patient leaflet
http://www.britishlivertrust.org.uk/home/the-liver/liver-diseases/hepatitis-b.aspx

Appendix 1: Investigations carried out first visit

Department	Investigation
Haematology	Blood test for: Full blood count Coagulation screen
Biochemistry	Blood tests for Liver function tests including GGT Urea & Electrolytes Ferritin *A*lpha-1-antitrysin Alpha-fetoprotein Caeruloplasmin (if <aged 40years) Thyroid function tests
Virology	Blood tests for Hepatitis B screen including HBeAg status (if cuurent result not available) Hepatitis A and C HIV (if appropriate) HBV DNA Hepatitis delta
Immunology	Auto-antibodies Serum immunoglobulins
Radiology	Abdominal Liver ultrasound Fibroscan

Appendix 2: Review of chronic hepatitis B patient

Frequency of review	Every 6/12 months
Tests	Routine weight Routine urinalysis
Physical review	Observe for signs of: • jaundice, • spider naevi, • ascites or peripheral oedema Ask patients: • if any episodes of confusion, haematemesis and malaena • any sustained unintentional weight loss • any new medical conditions (e.g. diabetes, heart failure, arthritis)
Clinical symptoms	Assess and provide guidance on: • Fatigue • Alcohol intake
Blood tests	FBC, coagulation Liver function tests including GGT Urea & Electrolytes Alpha-fetoprotein HB Viral DNA Hepatitis B screen
Investigations	Fibroscan yearly AFP and Ultrasound 6 monthly for • Asian men over age of 40 • Asian women over age of 50 • All patients with cirrhosis • Patients with family history of HCC • Africans over age of 20 • HBV/HIV co-infection
Current medications	Review and document current medications
Criteria for considering treatment	Rise in ALT > ULN HBV DNA > 2000iu/ml High score on Fibroscan suggestive of moderate fibrosis or cirrhosis Stage F2 metavir scoring on biospy