Management of chronic hepatitis B virus

In this article...
- Updated guidelines on treating patients with hepatitis B
- How the stages of CHB should be assessed
- Nurses’ roles in treatment and follow-up care

**Keywords:** Hepatitis B / Liver / Long-term conditions

This article has been double-blind peer reviewed

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**Abstract**

The management of chronic hepatitis B is complex due to its four disease stages. Monitoring is often required to inform future management; not all patients will require interventions. The long-term goals of treatment are to halt disease progression and to prevent cirrhosis, hepatocellular carcinoma and liver failure.

A number of guidelines are available, including those issued by the European Association for the Study of Liver Disease and recently published National Institute of Health and Care Excellence guidelines.

This article, the second in a two-part series, discusses the assessment and management of chronic hepatitis B in light of recent guidelines and the role of nurses in caring for patients with CHB. Part 1 looked at the prevalence and pathophysiology of chronic hepatitis B, recommendations for screening high-risk groups and immunisation.

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**Infectious diseases**

Recent updates to NICE guidance have provided clarity on how people with chronic hepatitis B should be assessed, treated and monitored after treatment

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**CHRONIC HEPATITIS B: PART 2 OF 2**

**5 key points**

1. NICE recommends initial assessments are carried out in primary care.

2. Patients with CHB need an initial assessment, usually followed by monitoring.

3. People with CHB are at risk of hepatocellular carcinoma and may need surveillance for this.

4. CHB is rarely cured, so goals of treatment are to halt disease progression and prevent liver failure, cirrhosis and HCC.

5. Nurses’ roles cover assessment, education, self-management, adherence, monitoring and providing support, advice and care.

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Hepatitis B is considered to be a dynamic disease as it can change over time and is thought to have four phases (Oakes, 2014):
- Immune tolerant phase;
- Immune clearance phase (immuno-active);
- Inactive carrier phase (immune control);
- Reactivation phase.

The management of chronic hepatitis B (CHB) is complex and a period of monitoring is often needed to inform the management of patients; those with inactive disease require lifelong monitoring.

**Guidelines**

A number of guidelines are available on the management of CHB, including the European Association for the Study of Liver Disease clinical practice guidelines (EASL, 2012) and the American Association for the Study of Liver Disease practice guidelines for the management of HBV (Lok and McMahon, 2009). Specialist centres in the UK have developed local guidance, while the National Institute for Health and Care Excellence recently published guidance on the diagnosis and management of CHB in children, young people and adults (NICE, 2013).

NICE (2013) recommends that all laboratory investigations and the initial liver ultrasound are carried out in primary care and the results sent to specialist centres with the referral. This differs from the existing model where the entire assessment takes place in hospital settings, usually at specialist centres.

**Assessment**

All patients with CHB should have a thorough initial assessment. A clinical history should be taken that includes ethnicity, place of birth, risk factors for acquiring the hepatitis B virus (HBV), family history of CHB or hepatocellular carcinoma (HCC), any previous HBV medication and any factors that could influence disease progression (Lee et al, 2010).

A physical examination should be carried out to look for signs and symptoms of fibrosions give accurate results in CHB patients with severe fibrosis and cirrhosis.
liver disease and all patients should have a baseline liver ultrasound. Laboratory investigations to check for other forms of liver disease or bloodborne viruses should be part of the initial assessment and include HBV serology (including geno-type), assessment of liver enzymes and hepatic function, metabolic liver disease screen, renal and bone profile, full blood count and INR (international normalised ratio), alpha-fetoprotein and co-infections with HIV, hepatitis C virus or hepatitis D virus (delta virus) (B Positive, 2008).

**Monitoring**

HBV can change over time, as some patients move through all four phases (Oakes, 2014). Those with HBeAg positive disease can seroconvert; this is where HBeAg is lost and HBeAb (the antibody to HBeAg) is formed. During some phases of CHB – such as in the immune active phase – levels of HBV DNA and liver enzyme alanine aminotransferase (ALT) fluctuate, so sequential measurements should be taken to inform disease management.

EASL (2012) and NICE (2013) have made recommendations for monitoring patients in the immune tolerant and immune control phases (Table 1).

Liver fibrosis assessment is essential when considering whether to start antiviral treatment of active CHB. There are two modalities – liver biopsy and the Fibroscan.

**Liver biopsy**

Liver biopsies are considered the gold standard in assessing fibrosis and necro-inflammation (inflammatory activity) levels; they may detect other forms of liver diseases concomitant with the HBV (Mani and Kleiner, 2009). However, the procedure is painful and invasive and has the potential for life-threatening complications and sampling errors (Maimone et al, 2009).

A number of scoring systems are used to interpret liver biopsy results, including the Metavir (fibrosis scale 0-4 and inflammatory scale 0-3) and Ishak scores (fibrosis score 0-6 and NI scale 0-18). The levels of fibrosis and necro-inflammation increase with rising scale scores in both systems.

**Fibroscan**

The Fibroscan (transient elastography) is being increasingly used as an alternative to liver biopsy or to help decide whether a patient needs a liver biopsy. It measures liver elasticity, giving a liver stiffness measurement (LSM) in kilopascals (kPa), which indicates the level of liver fibrosis. Fibroscans are quick to perform, convenient for patients, give instant results and are non-invasive, painless and highly accurate in CHB patients with severe fibrosis and cirrhosis (Marcellin et al, 2009).

However, Fibroscan readings increase with necro-inflammatory activity, in acute hepatitis, and during biochemical flares of hepatitis and cirrhosis (Wang et al, 2009), and may not be accurate in these circumstances. Severe obesity can affect readings, even with the use of an XL probe (Myers et al, 2012). Fibroscans cannot be used in pregnancy, in patients with ascites or where there is any type of swelling or fluid retention in the abdominal area.

NICE (2013) recommends Fibroscan as the initial test for liver disease in adults with CHB (Table 2).

**Treatment**

**Goals of treatment**

As most patients are asymptomatic, the long-term treatment goals are to stop disease progression and prevent cirrhosis, liver failure and HCC (Shamiyani et al, 2009). HBV is difficult to eradicate because its covalently closed circular DNA (cccDNA) becomes established in hepatocyte nuclei and incorporated into the host genome (Dienstag, 2008); it is controllable rather than curable. Durable viral suppression and E antigen seroconversion (HBeAg positive patients only), normalisation of ALT and histological improvement are considered to be good treatment outcomes (Hadziyanis, 2011).

NICE (2013) does not recommend using genotype testing to determine a plan of treatment in people with CHB, contrary to previous guidelines (Table 3).

Treatment choice for CHB should be based on a medical assessment of the risks and benefits, and should take into account whether women are of childbearing age. Safety, efficacy and drug resistance need to be considered (Dusheiko, 2013). All these factors must be discussed with patients so they can make informed decisions. Some advantages of the most commonly used antiviral agents, discussed below, should also be explained.

**Treatment during pregnancy**

The NICE guideline (2013) recommends:

- Tenofovir is offered to pregnant women with HBV DNA levels >10 E7 IU/ml in the third trimester to reduce the risk of HBV transmission to the baby;
- HBV DNA levels should be checked two months after starting tenofovir and the ALT levels should be checked monthly after birth to detect postnatal flares;
- Treatment can be discontinued 4-12 weeks after delivery, unless the mother meets the criteria for long-term treatment;
- Mothers may breastfeed while taking antiviral therapy.

**Antiviral agents**

**Pegylated interferon**

Pegylated interferon stimulates the immune system to attack the virus with the intention of making it inactive; it also has a mild antiviral action (Lau et al, 2005).

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**TABLE 1: RECOMMENDATIONS FOR MONITORING PATIENTS: IMMUNE TOLERANT AND IMMUNE CONTROL PHASES**

<table>
<thead>
<tr>
<th>Phase</th>
<th>EASL recommendations</th>
<th>NICE recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune tolerant (HBeAg positive)</td>
<td>Patients aged under 30 with normal ALT levels, high HBV DNA levels and no evidence of liver disease or family history of HBV or HCC do not require immediate liver biopsy or treatment but should have transaminases and HBV DNA monitored every 3-6 months</td>
<td>Monitor ALT levels every 24 weeks</td>
</tr>
<tr>
<td></td>
<td>Liver biopsy or treatment should be considered in patients aged over 30 years and/or with a family history of cirrhosis</td>
<td>Monitor ALT every 12 weeks on at least three consecutive occasions if there is an increase in ALT levels</td>
</tr>
<tr>
<td>Inactive carrier/immune control (HBeAg negative)</td>
<td>Patients with persistently normal ALT levels and HBV DNA levels greater than 2,000 IU/ml but less than 20,000 IU/ml with no evidence of liver disease should have close monitoring of HBV DNA levels (6-12 monthly) and ALT levels every three months for three years then lifelong monitoring (in case of reactivation)</td>
<td>Monitor ALT and HBV DNA levels every 48 weeks</td>
</tr>
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### Table 2. Fibroscan Scores and NICE Guidance

<table>
<thead>
<tr>
<th>Fibroscan Score</th>
<th>Level of Liver Fibrosis Indicated by Fibroscan</th>
<th>NICE Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver stiffness measurement (LSM) score ≥11kPa</td>
<td>Patients are likely to have cirrhosis</td>
<td>Offer antiviral treatment without a liver biopsy to adults with cirrhosis and detectable HBV DNA, regardless of HBeAg status, HBV DNA levels and ALT levels</td>
</tr>
</tbody>
</table>
| LSM 6-10kPa | Degree of fibrosis cannot be accurately predicted in this range. Some people may choose to have a liver biopsy in these circumstances to confirm the extent of the disease | Consider liver biopsy to confirm the level of fibrosis and offer antiviral treatment to:  
- Adults aged 30 years or over with HBV DNA >2,000IU/ml and abnormal ALT on two consecutive occasions three months apart  
- Adults younger than 30 years who have HBV DNA >2,000IU/ml and abnormal ALT on two consecutive tests conducted three months apart if there is evidence of necro-inflammation or fibrosis on biopsy or LSM >6.0kPa  
- Adults with cirrhosis and detectable HBV DNA regardless of HBeAg status, HBV DNA levels and ALT levels  
Consider antiviral treatment in adults with HBV DNA >2,000IU/ml and evidence of necro-inflammation or fibrosis on liver biopsy |
| LSM <6kPa  
- Aged <30 years and HBV DNA >2000IU/ml  
- Abnormal ALT on two consecutive tests conducted three months apart | Degree of fibrosis cannot be accurately predicted | Offer liver biopsy and proceed to antiviral treatment as per recommendations 1-4 above |
| LSM <6kPa  
- HBV DNA <2000 IU/ml  
- Normal ALT | Unlikely to have significant fibrosis | Do not offer liver biopsy or antiviral treatment |

Offer an annual reassessment of liver disease with a Fibroscan to adults who are not taking antiviral treatment

### Table 3. NICE Recommended Treatment Pathway

<table>
<thead>
<tr>
<th>HBeAg-positive Patients</th>
<th>HBeAg-negative Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td>Consider: 48 weeks pegylated interferon alfa 2a for all patients with compensated liver disease, irrespective of genotype*</td>
</tr>
<tr>
<td>Discontinue pegylated interferon at 24 weeks if HBV DNA has decreased &lt;2 logs and/or if HBsAg levels are &gt;20,000IU/ml, and offer second-line therapy</td>
<td>Consider discontinuation of pegylated interferon at 24 weeks if HBV DNA has decreased &lt;2 logs and if HBsAg levels have not decreased, and offer second-line treatment</td>
</tr>
<tr>
<td><strong>Second-line therapy</strong></td>
<td>Tenofovir for those who do not seroconvert or relapse. Offer entecavir as an alternative second-line treatment for those who cannot tolerate tenofovir</td>
</tr>
<tr>
<td>Offer tenofovir or entecavir</td>
<td>Offer tenofovir or entecavir</td>
</tr>
<tr>
<td>Detectable HBV DNA at 48 weeks</td>
<td>Review adherence, provide support in line with NICE (2009) guidance on medicines adherence</td>
</tr>
<tr>
<td>Consider switching from tenofovir to entecavir or from entecavir to tenofovir</td>
<td></td>
</tr>
<tr>
<td>Detectable HBV DNA at 96 weeks</td>
<td></td>
</tr>
</tbody>
</table>
- No lamivudine resistance – consider adding lamivudine to tenofovir  
- Lamivudine resistance – consider adding entecavir to tenofovir |
| HBsAg seroconversion | HBsAg seroconversion (loss of surface antigen and formation of surface antibodies) and undetectable HBV DNA |
| Consider stopping oral antiviral medication at 12 months in non-cirrhotic patients only | Consider stopping oral antiviral medication at 12 months in non-cirrhotic patients only |

*Avoid in pregnancy unless the potential benefit outweighs the risk; women of childbearing age must use effective contraception throughout therapy
It is a fixed course but has more side-effects than oral medications, including flu-like symptoms, anorexia and weight loss, depression and bone marrow suppression (Pomfret and Wong, 2007).

Pegylated interferon is contraindicated in some patients, such as those with severe depression or uncontrolled epilepsy (Dusheiko, 2013), so patients should be fully assessed before it is considered.

In HBeAg-positive patients, pre-treatment predictors of HBeAg seroconversion and HBsAg loss include if patients have:
» Genotype A or B (rather than C or D);
» High activity scores on liver biopsy;
» High serum ALT levels;
» Low viral load (HBV DNA level less than 2 x 10^8 IU/ml);

There are no clear pre-treatment predictors of response in HBeAg-negative patients. See part one of this series (Oakes, 2014) for an explanation of HBeAg positive and negative status.

Pegylated interferon is administered by weekly injection for 48 weeks, and patients need to be closely monitored by a clinical nurse specialist. Those who have completed a course need to be monitored for the long term by a nurse specialist or doctor.

Oral antiviral agents
Tenoforv (a nucleotide analogue) and entecavir (a nucleoside analogue) are safe and potent medicines with high genetic barriers to resistance. These medications are taken as a single therapy, in tablet form once daily, and interrupt the HBV lifecycle by inhibiting viral polymerase, which is essential for viral replication.

The advantages of oral agents are that they have fewer side-effects, such as headaches and occasional nausea, than pegylated interferon. However, they need to be taken for many years, if not for life.

In HBeAg-positive CHB, pre-treatment factors that may predict HBeAg seroconversion are:
» Low viral load (HBV DNA level less than 2 x 10^8 IU/ml);
» High serum ALT levels;
» High activity scores on liver biopsy.

Monitoring and support
Patients receiving pegylated interferon need to be shown how to administer their injections and attend regular clinic visits (usually monthly) to collect medication and manage side-effects. Blood samples should be taken at each visit for full blood counts and biochemical profiles, with periodic thyroid function, auto-antibody and immunoglobulin tests. Serological markers should be taken before, during and after treatment.

Patients receiving oral antiviral agents need to attend every six months once they are established on treatment; blood samples should be taken to check full blood count, liver and renal profiles, and biochemical profiles, with periodic thyroid function, auto-antibody and immunoglobulin tests. Serological markers should be taken before, during and after treatment.

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HCC screening
Although cirrhosis is a risk factor for HCC, it can occur if cirrhosis is not present (Elgouhari et al, 2008). Table 5 shows the groups recommended to have routine HCC screening, 6-12 monthly liver ultrasound scans and alpha-fetoprotein measurement.

Nursing care
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Patients receiving oral antiviral agents need to attend every six months once they are established on treatment; blood samples should be taken to check full blood count, liver and renal profiles, and response to treatment. Adherence to medications should be checked and reinforced at each visit and advice on adherence measures should be given if needed.

HCC screening should be timed to fit in with clinic visits.

Education
Patients living with long-term conditions are encouraged to self-manage where possible (DH, 2009). However, those with CHB often lack self-care knowledge (Lan Huong et al, 2012). All patients with CHB should receive individualised
and religious beliefs, using an interpreter

pegylated interferon or oral medication,

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TABLE 5. ROUTINE HCC SCREENING: RECOMMENDED GROUPS

<table>
<thead>
<tr>
<th>AASLD recommendations</th>
<th>NICE recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• African men and women over the age of 20 years</td>
<td>• Metavir greater than or equal to F2, Ishak &gt;F3 or cirrhosis</td>
</tr>
<tr>
<td>• Asian men over the age of 40 years</td>
<td>• People without significant fibrosis (Metavir/ishak) as above if person is older than 40 years and family history of HCC and HBV DNA &gt;20 000 IU/ml</td>
</tr>
<tr>
<td>• Asian women over the age of 50 years</td>
<td>• Do not offer HCC surveillance in people aged under 40 without significant fibrosis or cirrhosis who have HBV DNA &lt;20,000IU/ml</td>
</tr>
<tr>
<td>• Anyone with cirrhosis</td>
<td></td>
</tr>
<tr>
<td>• Anyone with a family history of HCC</td>
<td></td>
</tr>
<tr>
<td>• Anyone over the age of 40 with a persistent or intermittently elevated ALT and/or HBV DNA level &gt;2,000IU/ml</td>
<td></td>
</tr>
</tbody>
</table>

NICE (2013); Lok et al (2009)

education on the following:
» Modes of HBV transmission, how to avoid onward transmission, and the need for testing and vaccination of close household contacts, sexual partners and direct family members;
» The dynamic nature of HBV meaning regular clinic visits for monitoring may be needed; how often they need to visit;
» Blood tests and their significance so patients understand the importance of attending clinic;
» The stages of CHB, its long-term effects on the liver, and that the absence of symptoms does not correlate with disease progression;
» The need for HCC screening with six-monthly liver ultrasounds and AFP measurements;
» Alcohol use, cigarettes and herbal medicines, remedies or teas – NICE (2013) recommends that other lifestyle issues, such as weight management and a healthy diet, are discussed;
» Monitoring and treatment in pregnancy and the need for babies to be vaccinated. Patients starting treatment with pegylated interferon or oral medication, should be educated about:
» The risks and side-effects;
» Short- and long-term treatment goals, and the fact that HBV is usually controllable but not curable;
» The duration of treatment – 48 weeks for pegylated interferon and probably lifelong for oral antiviral agents;
» Pegylated interferon – collection and storage of doses, when to take them, rotation of injection sites, disposal of sharps, avoidance during pregnancy and breastfeeding, common remedies to alleviate side-effects;
» Oral antiviral agents – how often to take tablets and whether this should be with food, renal monitoring with tenofovir, adherence, resistance and advice on pregnancy or breastfeeding.

Education should use simple terminology and take into account cultural needs and religious beliefs, using an interpreter if needed. Patients should be given written information in their own language and made aware of community groups, forums or resources that may help. Patients, families and carers should be given a personalised care plan outlining proposed treatment and long-term management (NICE, 2013).

Conclusion
CHB management remains complex, with many areas subject to debate. The NICE guideline should be used in the context of clinician experience and the patient’s condition and wishes. New developments being trialled will add to the complexity of CHB management but will also enhance care.
A crucial, ongoing element of nurses’ roles will be to give people with CHB up-to-date information so they can make informed decisions.

NICE proposes that CHB patients’ initial investigations take place in primary care. This will require systems being put in place in the community and GPs engaging with specialist services. If this is achieved, a logical progression would be for those in the immune control phase (who make up the largest proportion of CHB patients and have a low complexity) to move towards a more community-based model of care, along with other non-complex CHB patients.

References