HAUTE AUTORITÉ DE SANTÉ

GUIDE FOR DOCTORS : LONG-TERM CONDITIONS

CHRONIC HEPATITIS B

July 2007

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This document was validated by the HAS Board in July 2007.

Contents

Updated ALD Guides and Lists

Guides for doctors developed by HAS are revised every three years.

In the meantime, the list of procedures and services (LAP) is revised, at minimum, on a yearly basis. This list is available on the HAS website.
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1. Introduction

The management of hepatitis B is a major challenge for public health. A recent InVS[1] descriptive study has provided new estimates for the prevalence of HB surface antigen (HbsAg) carriage. The presence of this antigen confirms chronic infection with the hepatitis B virus (HBV). The study showed that in France, an estimated 300,000 people (0.84% of the population) are currently HBsAg carriers. Hepatitis B is transmitted sexually, by direct contact with HBV infected blood, or by vertical (maternal/fetal) transmission. Even though the risk of transmission by blood transfusion has been eliminated. However, the risk in intravenous drug users is still substantial. In the InVS[1] study, more men than women were HBsAg carriers (1.19% vs 0.16%). In addition, only half of HBsAg carriers knew they were seropositive.

Initial infection with HBV is most often asymptomatic but, in 0.1% to 1% of acute cases, it may develop into fulminant hepatic failure, which is often fatal in the absence of liver transplantation. After the acute episode, which may or may not be symptomatic, hepatitis B becomes chronic in 2 to 10% of cases. There is the risk that it may lead to cirrhosis and/or hepatocellular carcinoma. The current challenge is vaccination of at-risk subjects, screening, and management of infected patients in order to prevent complications.

Antiviral drugs active against HBV are available. The main aim of treatment is to prevent virus replication. However, as these drugs are not consistently effective and as they cause side-effects, health professionals generally agree that the most active forms of the disease should be treated and that the most stable forms should be monitored without treatment. The more stable forms can in fact remain inactive for a long time. However, patients do need to be monitored regularly and the indication for treatment should be reconsidered if the disease progresses.

This guide is intended as a practical reference tool for primary care doctors managing hepatitis B. Its content has been discussed and validated by a multidisciplinary working group. It is a practical summary of available clinical practice and/or consensus conference guidelines and of expert opinion (when no relevant data were available to draw guidelines). Expert opinion is needed in fields such as patient follow-up when the pattern of surveillance is based on consensus among professionals rather than on comparative data obtained from clinical trials.

An ALD guide cannot be comprehensive, i.e. cover all comorbidities, treatment details, hospital care protocols, etc. It does not claim to cover all the ways of managing HBV, nor does it discharge doctors from their individual responsibility to their patient. It just describes the basic framework of care. It will be updated as new data are validated.

[1] InVS: French Institute for Healthcare Monitoring

2. Initial assessment

Tests to diagnose fibrosis are being assessed by HAS (2006 work programme) and could reduce the indications for liver biopsy (LB). This guide will be updated once the results of the assessment are available.

2.1 Main aims

- Confirm the patient is a chronic HBV carrier and establish whether the disease is active or not.
- With a view to antiviral therapy:
- assess the indication for treatment;
- identify comorbidities, impact of possible addictions (alcohol, drugs, tobacco), and any contraindications to antiviral therapy;
- inform the patient of the benefits of antiviral therapy, but also mention its inherent drawbacks and possible complications.
- If antiviral treatment is not initiated, record basic data in case of subsequent complications.

2.2 Professionals involved

- The primary care doctor and/or specialist (hepatologist, infectious diseases physician, specialist in internal medicine) confirm the diagnosis and assess the patient. A specialist should perform the liver biopsy (LB).
- Ophthalmologist: during the initial work-up if the patient has any risk factors.
- A psychiatric assessment is essential at the time of the initial work-up if the patient has a history of psychiatric problems or depression.
- Children should undergo special monitoring (if possible by a specialised team) that is coordinated by the primary care doctor. Treatments have not been sufficiently validated in children (not part of marketing authorisation) and should be prescribed as part of a trial.

2.3 Investigations

Initial work-up and tests for comorbidities are given in Table 1 on the next page.

Look for contraindications to the use of interferon:

- Laboratory test for pregnancy.
- ECG in patients over the age of 40 or with known heart disease.
- Eye examination to test for xerophthalmia if symptoms are present.
- Psychiatric assessment (mandatory if patient has psychiatric problems).

Table 1. Initial work-up and tests for co-morbidities

Objective	Test
Diagnosis of chronic HBV carriage and positive HbeAg	HBsAg persisting more than 6 months IgM antibodies to HBc to distinguish acute hepatitis (IgM HBc positive) from chronic hepatitis (IgM HBc negative) HBeAg, HBeAb
Assessment of HBV activity	HBV DNA > 100 000 copies/ml for HBeAg positive chronic hepatitis HBV DNA > 10 000 copies/ml for HBeAg negative chronic hepatitis Repeat viral level tests may be needed to confirm absence of significant viral multiplication (because of frequently fluctuating viral levels during chronic hepatitis B)
Assessment of chronic hepatitis activity	Transaminases (ASAT, ALT) Liver biopsy (LB) including METAVIR[1] score Confirmation of histological lesions of chronic active hepatitis by LB is usually recommended
Diagnosis of co-infections	Serological tests HIV, HCV (HCV antibodies), HDV (delta virus antibodies) Serological tests HAV (IgG antibody to HAV)
Other laboratory and diagnostic tests	Gamma-GT, alkaline phosphatases, bilirubin, prothrombin time (PT), full blood count including platelets Alphafoetoprotein Abdominal ultrasound
Tests for comorbidities	TSH thyroid peroxidase autoantibodies (TPOAb), antinuclear autoantibodies, anti smooth muscle and anti-LKM1 antibodies if interferon treatment is likely Serum creatinine, proteinuria, creatinine clearance, serum albumin level Blood glucose Total cholesterol, triglycerides, HDL-cholesterol if there is steatosis Transferrin saturation to screen for haemochromatosis

[1] The METAVIR score measures the histology of the liver.

3. Management and treatment

3.1 Aims

- Reduce HBV DNA to < 100 000 copies/ml for HBeAg positive chronic hepatitis, and to < 10 000 copies/ml for HBeAg negative chronic hepatitis.
- Restore normal transaminase values, stabilize, and if possible reduce histological lesions.
- Obtain HBe antigen seroconversion if HBeAg positive hepatitis, and (less frequently) HBsAg seroconversion.

3.2 Professionals involved

Antiviral therapy should be initiated by a specialist (hepatologist, infectious diseases physician, specialist in internal medicine). If the patient is known to be coinfected with HBV-HIV, it is important to consult an infectious diseases specialist.

3.3 Patient education and lifestyle changes

► Structured patient education

The aim of patient education is to ensure that a patient with chronic hepatitis B has a good understanding of their disease and mastery of the technical procedures required. Patient education should include:

- information covering the benefits of available treatments, the possible side effects of any treatment the patient may receive, the need for good long-term compliance (particularly for nucleotide therapy), the scheduling of routine tests and of any screening tests for complications, and the results obtained in these tests;
- learning to perform technical procedures (self-injection if the patient is on interferon).

► Lifestyle changes

- Patients should give up alcohol or, if this is not possible, they should reduce their intake considerably.
- Patients should give up smoking, and if necessary they should receive support while doing so. Patients who remain dependent may be given appropriate medication. First-line therapy is nicotine replacement (patches, gum, lozenges, inhaler), with bupropion as second-line therapy. Patients who are highly dependent, who are addicted to multiple substances, or who have anxiety or depression, should see a specialist.

- Overweight patients should try and lose weight. Lipid profiles and blood glucose should be normalised, especially if patients have hepatic steatosis.

► Other preventive measures

- Women of childbearing age should use contraception throughout antiviral treatment. This also applies to treated men and their partners. Men whose partners are pregnant should be told that they must use a condom.

3.4 Treatments (Table 2)

Antiviral drugs with a Marketing Authorisation	◗ Interferon (IFN) alpha ◗ Pegylated interferon (PEGIFN) alpha-2a or pegylated interferon alpha-2b ◗ Lamivudine Adefovir
Other types of drugs	◗ Nicotine replacement or bupropion, to help the patient stop smoking (see Lifestyle changes above) Oral contraceptives, if a woman may become pregnant during antiviral treatment (see Other preventive measures above)
Vaccination[1]	Vaccinate against HBV and HVA if anti-HVA IgG antibodies are negative
Liver transplantation	If severe cirrhosis (Child-Pugh C) or hepatocellular carcinoma (single lesion ≤ 5 cm or ≤ 3 nodules each ≤ 3 cm).

[1] Vaccination against hepatitis B is recommended for parents, brothers and sisters, and sexual partners

4. Follow-up

4.1 Aims

- To assess efficacy and safety in patients receiving treatment.
- To monitor change in cytolysis, cholestasis, fibrosis and hepatocellular insufficiency, and to screen for hepatocellular carcinoma.
- To check that there is no progressive liver disease in untreated patients and non-responders.

4.2 Professionals involved

- The primary care doctor may issue repeat prescriptions and be in charge of follow-up, but should discuss the case with a specialist, particularly at weeks 12, 24 and 48, to see if treatment needs to be adjusted.
- The primary care doctor should have knowledge of and recognise common side effects of antiviral therapy which may require referral to a specialist (e.g. haematologist, psychiatrist, cardiologist, endocrinologist, ophthalmologist, dermatologist, chest physician).
- A nurse is needed when the patient cannot perform injections and for structured patient education (learning injection technique (for IFN or IFN PEG), managing drugs, managing side-effects, and compliance).

Except in special situations (in the case of certain comorbidities or side effects requiring further assessments), patients on antiviral therapy with interferon should see their doctor or a specialist every 4 weeks during treatment and during the 6 months following treatment, and every 3 months thereafter. Patients on nucleotide therapy are usually seen every 3 months.

4.3 Further investigations

► Investigations to be performed during treatment

Table 3 gives the lab tests to be performed during treatment.

Table 3. Lab tests during treatment

Treatment	Lab tests	Periodicity
IFN alpha or IFN PEG	Transaminases and full blood count including platelets TSH	15 days, then 1 month after treatment initiation, thereafter monthly Every 3 months
Lamivudine	Transaminases	Every 3 months
Adefovir	Transaminases. Serum creatinine, with creatinine clearance if renal failure is a risk factor	Every 3 months Every 3 months

During treatment, HBV DNA should be monitored every 3 months irrespective of HBeAg status. Table 4 shows how viral load should be monitored if DNA HBV falls below < 100 000 copies/ml.

Table 4. Viral load monitoring during treatment (if fall in DNA HBV is < 100 000 copies/mL)

Patients	Situation	Test	Periodicity
- in patients initially HBeAg positive	◗ In all cases	◗ HBeAg	◗ Every 6 months
	◗ If HBeAg negative, look for HbeAb	◗ HBeAg and HBeAb	◗ Every 6 months
	◗ If HBeAb positive (HBe sero-conversion)	◗ HBsAg	◗ Every 6 months
	◗ If HBsAg negative, look for HbsAb	◗ HbsAg and HBsAb	◗ Every 6 months
	◗ If HbsAb positive (HBs sero-conversion)	◗ Monitor sero-conversion	◗ Every 3 months for first year, then as decided by the specialist
- in patients HBeAg negative (HBeAb positive)	◗ In all cases	◗ HBsAg	◗ Every 6 months
	◗ If HBsAg negative, look for HBsab	◗ HBsAg and HBsAb	◗ Every 6 months
	◗ If HBsAb positive (HBs sero-conversion)	◗ Monitor sero-conversion	◗ Every 3 months for first year, then as decided by the specialist

Specific consultations and follow-up

Antiviral drugs can cause side effects (anaemia, neutropenia, thrombopenia, thyroid dysfunction psychiatric symptoms, skin disorders, etc.). The patient may need to be referred to a specialist.

► Investigations to be performed after interferon treatment (Table 5)

Table 5. Lab tests and viral load monitoring after treatment with IFN alpha or IFN PEG

Lab tests	Viral load monitoring	
Transaminases every 3 months	HBV DNA every 3 months for 1 year, then every 6 months	
	If HBV DNA falls < 100 000 copies/ml	HBeAg.
	If HBeAg negative	HBeAb, HBsAg and HBsAb
	If HBeAb positive (HBe seroconversion)	HBsAg and HBsAb.
	If HBeAg positive, seroconversion may be delayed depending on the situation, serological tests may need to be repeated during treatment	

► Investigations to be performed in untreated patients (Table 6)

- In addition to the tests shown in Table 6, an abdominal ultrasound should be performed every year, except in cirrhotic patients or patients with severe chronic hepatitis (see below).

Table 6. Lab tests and viral load monitoring in untreated patients

Lab tests	Viral load monitoring
Transaminases every 3 months for the first year, then every 6 months. Gamma-GT and prothrombin time every 6 months Alpha-foetoprotein every year, except in cirrhotic patients or patients with severe chronic hepatitis (see below).	HBV DNA and HBeAg every year

► Investigations to be performed in cirrhotic patients or patients with severe chronic hepatitis (stage F3-F4[1])

- Follow-up (as described above) should be increased when screening for hepatocellular cancer.
- Gastrooesophageal varices should be monitored.
- Abdominal ultrasound and alpha-foetoprotein every 6 months.
- Upper gastrointestinal endoscopy every 1–3 years. Frequency depends on the clinical context, in particular the size of gastrooesophageal varices.

[1] The METAVIR score measures the histology of the liver. The F classification (F0 – F4) measures fibrosis. Stages F3-F4 designate pre-cirrhotic to cirrhotic conditions, respectively

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