NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

SCOPE

Clinical guideline title: Hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults

Quality standard title: Hepatitis B (chronic)

1 Introduction

1.1 Clinical guidelines

Clinical guidelines are recommendations by NICE on the appropriate treatment and care of people with specific diseases and conditions within the NHS. They are based on the best available evidence.

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

1.2 Quality standards

Quality standards are a set of specific, concise quality statements and measures that act as markers of high-quality, cost-effective patient care, covering the treatment and prevention of different diseases and conditions.

For this topic a NICE quality standard will be produced based on the guideline recommendations. The clinical guideline and the quality standard will be published at the same time.

This scope defines the areas of care for which specific quality statements and measures will (and will not) be developed.

The guideline and quality standard development processes are described in detail on the NICE website (see section 8).

2 Need for guidance

2.1 Epidemiology

a) Chronic hepatitis B is usually defined as hepatitis B infection that continues for longer than 6 months. It is usually indicated by persisting positivity for hepatitis B surface antigen (HBsAG). However, people who have recovered following hepatitis B virus infection may, if immunosuppressed, become HBsAg positive again. Chronic hepatitis B virus infection is a major healthcare problem in the UK, with an estimated prevalence of 0.3%. Approximately 180,000 people in the UK have the condition. Its prevalence is considerably higher among high-risk groups such as first generation migrants from areas where hepatitis B is endemic; people who have multiple sexual partners; and injecting drug users. The incidence of hepatitis B has risen sharply, from 435 new cases in 1990 to 1151 in 2003.

b) Currently, there are approximately 600 to 800 new cases of symptomatic (jaundiced) acute hepatitis B infection in the UK each year. In 50% of cases there is no obvious risk factor; 20% of cases relate to intravenous drug use; and 25% are sexually acquired (80% of these in men who have sex with men). In the remaining cases the infection is thought to have been transmitted from people with chronic hepatitis B who are asymptomatic.

c) The risk of an acute infection progressing to a chronic infection is closely related to age at acquisition, and varies from 5% in adulthood to more than 90% in perinatal infection.

d) Chronic hepatitis B most commonly follows childhood infection, and thus people often present to health services after many years of asymptomatic infection (often unknown to the patient).

e) Treatment is needed for those at highest risk of progressive liver disease and its complications. It aims to primarily reduce viral loads and bring about HBsAg loss. Multiple studies have shown that therapeutic reduction in viral loads leads to a marked reduction in hepatic inflammation, fibrosis progression and risk of cirrhosis. Among people who already have cirrhosis the risk of liver complications, including hepatocellular carcinoma, is also reduced.

f) Currently, no long-term studies of the clinical outcome for the most recently approved nucleoside or nucleotide analogue treatments are available. However, early studies (that have been running for up to 5 years) suggest that these treatments have the most potent effect on viral loads and liver histology, and are likely to have the greatest impact on complications associated with hepatitis B infection.

2.2 Current practice

a) Diagnosing chronic hepatitis B infection includes the use of immunoassays for HBsAg, hepatitis B ‘e’ antigen (HBeAg), and antibodies to hepatitis B ‘e’ antigen (HBeAb). People with hepatitis B may be either HBeAg positive or negative. Chronic hepatitis B infection may also be diagnosed using quantitative and qualitative hepatitis B virus DNA assays. Co-infections with hepatitis C, hepatitis D and HIV are identified by serological assay.

b) To assess the phase of chronic hepatitis B, routine liver function tests are performed. Serological assays are used to detect HBeAg and HBeAb. Molecular assays to measure hepatitis B virus DNA are also undertaken.

c) Two classes of drug are currently used to treat chronic hepatitis B infection: pegylated interferon and nucleoside or nucleotide analogues. Four nucleoside or nucleotide analogues are currently recommended by NICE and are in widespread clinical use.

d) Pegylated interferon suppresses the virus in a smaller proportion of patients than nucleoside or nucleotide analogues (especially entecavir and tenofovir) but is given for a fixed duration of 48 weeks. In contrast, nucleoside or nucleotide analogues often need to be used as long-term treatment.

e) If needed, nucleoside or nucleotide analogue therapy may be given after pegylated interferon.

f) Combination nucleoside or nucleotide analogue treatment may be necessary to reduce the risk of, or to treat, any type of established resistance to treatment.

g) The earliest licensed nucleoside or nucleotide analogues (lamivudine and adefovir) appear to be less effective than the more recently approved agents (entecavir and tenofovir), judged according to patient seroconversion rates, rates of resistance, and the proportion of patients achieving undetectable viral loads.

h) Telbivudine is licensed for treating hepatitis B but is not recommended by NICE (NICE technology appraisal guidance 154).

i) Tenofovir in combination with emtricitabine is used in some people with chronic hepatitis B, but is licensed at present only for HIV infection.

j) 'Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B' (NICE technology appraisal guidance 96), compares interferon, lamivudine, and adefovir, but otherwise NICE guidance considers each drug for hepatitis separately.

k) Patient information and counselling offered to family members and/or sexual partners by healthcare professionals should include treatment options, the risk of other family members and/or sexual partners being infected, and the benefits of vaccination against the hepatitis B virus.

l) Several audits have shown significant variation in practice. For example, a recent audit in London showed that only two-thirds of people with chronic hepatitis B infection diagnosed in primary care were referred for assessment. There is also strong anecdotal evidence of wide variation in prescribing practice with regard to initial choice of agents and duration of therapy, particularly after HBeAg or HBeAb seroconversion. This guideline is needed to reduce variation in practice and improve the care of people with chronic hepatitis B.

3 Clinical guideline

3.1 Population

3.1.1 Groups that will be covered

a) Children, young people and adults with chronic hepatitis B virus infection including:

- people co-infected with hepatitis C or hepatitis delta (D) virus
- immunocompromised people (such as those undergoing cancer treatments) who are carriers or have been previously infected, for whom prophylactic treatment might be beneficial
- pregnant and lactating women
- people with cirrhosis, including those with liver decompensation.

3.1.2 Groups that will not be covered

a) People who have had a liver transplant.

b) People with acute hepatitis B.

c) People co-infected with HIV.

3.2 Healthcare settings

a) Primary, secondary, tertiary and community NHS settings.

3.3 Diagnosis and management

3.3.1 Key issues that will be covered

Identification and assessment of chronic hepatitis B

a) Healthcare setting for pre-therapeutic tests in people found to be hepatitis B antigen positive (HBeAg, HBeAb, quantitative HBsAg, and hepatitis B virus DNA), for example in primary or secondary care.

b) Criteria for referral to specialist services.

c) Laboratory tests to determine severity of necro-inflammatory activity, fibrosis (grade/stage) and whether or not treatment needs to be started:

- liver biopsy
- non-invasive methods of assessing liver fibrosis (for example, serum fibrosis markers, elastography, aspartate aminotransferase/platelet ratio index [APRI]).

d) Diagnosis of concomitant infections, heptatitis C and hepatitis delta (D) virus.

Pharmacological treatment

e) Sequential and combination drug therapy for specified subgroups:

- adefovir
- emtricitabine (in combination with tenofovir)
- entecavir
- lamivudine
- pegylated alpha-interferon
- telbivudine
- tenofovir.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by

evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

Monitoring stages of the condition

f) Surveillance timing, and frequency of:

- quantitative DNA assays and resistance genotyping
- adverse events, for example renal toxicity
- hepatitis B markers (HBeAg, hepatitis B virus DNA, HBsAg) as stopping points for treatment
- quantitative HBsAg by serology
- case finding for hepatocellular carcinoma.

g) Patient information

3.3.2 Key issues that will not be covered

a) Primary prevention of hepatitis B, including vaccination.

b) Case finding.

c) Signs and symptoms of advanced hepatitis B with cirrhosis.

d) Non-pharmacological management of chronic hepatitis B.

e) Co-infection of chronic hepatitis B with HIV or hepatitis viruses A or E.

f) Guidance on working practices for infected healthcare workers.

g) Liver transplantation.

h) Acute hepatitis B.

3.4 Main outcomes

a) Reduction of serum hepatitis B DNA, tested by the most sensitive available quantitative assay

b) Clearance of HBeAg and seroconversion forHBeAb.

c) Clearance of HBsAg and seroconversion forHBsAb.

d) Regression of hepatic inflammation and fibrosis grade/stage.

e) Frequency of liver decompensation

f) Incidence of hepatocellular carcinoma.

g) Quality of life, tested using a validated general instrument or a validated liver disease-specific instrument.

h) Mortality.

i) Adverse effects.

j) Rates of vertical transmission from mother to infant for pregnant and lactating women.

k) Resistance

3.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see section 8).

4 Quality standard

Information on the NICE quality standards development process is available on the NICE website, see section 8.

4.1 Areas of care

The areas of care of a patient's journey that will inform the development of the quality statements are set out below (see 4.1.1). The content of the final quality standard statements may differ before and after consultation with stakeholders.

4.1.1 Areas of care that will be considered

Identification and assessment of chronic hepatitis B

a) Case finding strategies (from Hepatitis B and C: ways to promote and offer testing. NICE public health guidance. Publication expected December 2012)

b) Healthcare setting for pre-therapeutic tests in people found to be hepatitis B antigen positive (HBeAg, HBeAb, quantitative HBsAg, and hepatitis B virus DNA).

c) Criteria for referral to specialist services

d) Laboratory tests to determine severity of necro-inflammatory activity, fibrosis (grade/stage) and whether or not treatment needs to be started

e) Diagnosis of concomitant infections, heptatitis C and hepatitis delta (D) virus.

Pharmacological treatment

f) Pharmacological treatment for management of chronic hepatitis B including sequential and combination therapies for specific subgroups.

Monitoring stages of the condition

g) Monitoring of chronic hepatitis B including timing and frequency of tests on and off treatment

h) Patient information.

4.1.2 Areas of care that will not be considered

a) Primary prevention of hepatitis B including vaccination

b) Signs and symptoms of hepatitis B.

c) Non-pharmacological management of chronic hepatitis B.

d) Co-infection of chronic hepatitis B with HIV or hepatitis viruses A or E.

e) Guidance on working practices for infected healthcare workers.

f) Liver transplantation.

g) Acute hepatitis B.

4.2 Economic aspects

Developers will take into account both clinical and cost effectiveness when prioritising the quality statements to be included in the quality standard. The economic evidence will be considered, and the cost and commissioning impact of implementing the quality standard will be assessed.

5 Status

5.1 Scope

This is the final scope.

5.2 Timings

The development of the guideline recommendations and the quality standard will begin in September 2011.

6 Related NICE guidance

6.1.1 NICE guidance that will be incorporated in or updated by the clinical guideline

This guideline will incorporate the following NICE guidance:

- Tenofovir disoproxil for the treatment of chronic hepatitis B. NICE technology appraisal guidance 173 (2009). Available from www.nice.org.uk/guidance/TA173
- Telbivudine for the treatment of chronic hepatitis B. NICE technology appraisal guidance 154 (2008). Available from www.nice.org.uk/guidance/TA154
- Entecavir for the treatment of chronic hepatitis B. NICE technology appraisal guidance 153 (2008). Available from www.nice.org.uk/guidance/TA153
- 1.1 of Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. NICE technology appraisal guidance 96 (2006). Available from www.nice.org.uk/guidance/TA96

This guideline will update the following NICE guidance:

- 1.2 - 1.4 of Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. NICE technology appraisal guidance 96 (2006). Available from www.nice.org.uk/guidance/TA96

6.2 Related NICE guidance

Published

- Increasing the uptake of HIV testing among men who have sex with men. NICE public health guidance 34 (2011). Available from: www.nice.org.uk/guidance/PH34
- Increasing the uptake of HIV testing among black Africans in England. NICE public health guidance 33 (2011). Available from: www.nice.org.uk/guidance/PH33
- Alcohol-use disorders. NICE clinical guideline 115 (2011). Available from www.nice.org.uk/guidance/CG115
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Obesity NICE clinical guideline 43 (2006). Available from www.nice.org.uk/guidance/CG43

NICE guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Patient experience in generic terms. NICE clinical guideline. Publication expected October 2011.
- Hepatitis B and C: ways to promote and offer testing. NICE public health guidance. Publication expected December 2012.

7 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual'
- 'Developing NICE quality standards: interim process guide'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual and

www.nice.org.uk/aboutnice/qualitystandards). Information on the progress of the guideline and quality standards is also available from the NICE website (www.nice.org.uk).