NICE National Institute for Health and Care Excellence

NICE guideline

Hepatitis B (chronic): diagnosis and management

Clinical guideline
Published: 26 June 2013
Last updated: 20 October 2017

www.nice.org.uk/guidance/cg165

Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guideline partially replaces TA96.

This guideline is the basis of QS65 and QS152.

Overview

This guideline covers assessing and managing chronic hepatitis B in children, young people and adults. It aims to improve care for people with hepatitis B by specifying which tests and treatments to use for people of different ages and with different disease severities.

Who is it for?

- Healthcare professionals
- Commissioners and providers
- People with chronic hepatitis B and their families and carers

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

The following guidance is based on the best available evidence. The full guideline gives details of the methods and the evidence used to develop the guidance.

In this guideline, children and young people are defined as aged up to 18 years. Please follow the recommendations for women who are pregnant for young people with chronic hepatitis B who are pregnant.

1.1 Patient information

1.1.1 Provide information on the following topics to people with chronic hepatitis B and to family members or carers (if appropriate) before assessment for antiviral treatment:

- the natural history of chronic hepatitis B, including stages of disease and long-term prognosis
- lifestyle issues such as alcohol, diet and weight
- family planning
- monitoring
- routes of hepatitis B virus (HBV) transmission
- the benefits of antiviral treatment, including reduced risk of serious liver

disease and death and reduced risk of transmission of HBV to others

- treatment options and contraindications based on the patient's circumstances, including peginterferon alfa-2a and nucleoside or nucleotide analogues
- short- and long-term treatment goals
- causes of treatment failure, including non-adherence to prescribed medicines, and options for re-treatment
- risks of treatment, including adverse effects and drug resistance.

1.1.2 Offer a copy of the personalised care plan to people with chronic hepatitis B and to family members or carers (if appropriate) outlining proposed treatment and long-term management, for example, a copy of the hospital consultation summary.

1.1.3 Provide information on self-injection techniques to people beginning peginterferon alfa-2a or to family members or carers.

1.1.4 NICE has produced public health guidance on ways to promote and offer testing to people at increased risk of infection with hepatitis B. All healthcare professionals should follow the recommendations in the NICE guideline on hepatitis B and C testing.

1.1.5 NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in the NICE guideline on patient experience in adult NHS services.

1.2 Assessment and referral in primary care

Adults who are HBsAg positive

1.2.1 Arrange the following tests in primary care for adults who are hepatitis B surface

antigen (HBsAg) positive:

- hepatitis B e antigen (HBeAg)/antibody (anti-HBe) status
- HBV DNA level
- IgM antibody to hepatitis B core antigen (anti-HBc IgM)
- hepatitis C virus antibody (anti-HCV)
- hepatitis D virus antibody (anti-HDV)
- HIV antibody (anti-HIV)
- IgG antibody to hepatitis A virus (anti-HAV)
- additional laboratory tests including alanine aminotransferase (ALT) or aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum albumin, total bilirubin, total globulins, full blood count and prothrombin time
- tests for hepatocellular carcinoma (HCC), including hepatic ultrasound and alpha-fetoprotein testing.

1.2.2 Refer all adults who are HBsAg positive to a hepatologist or to a gastroenterologist or infectious disease specialist with an interest in hepatology.

1.2.3 Include the results of the initial tests with the referral (see recommendation 1.2.1).

Pregnant women who test HBsAg positive at antenatal screening

1.2.4 Refer pregnant women who are HBsAg positive to a hepatologist, or to a gastroenterologist or infectious disease specialist with an interest in hepatology, for assessment within 6 weeks of receiving the screening test result and to allow treatment in the third trimester (see recommendation 1.5.35 in the section on women who are pregnant or breastfeeding).

Adults with decompensated liver disease

1.2.5 Refer adults who develop decompensated liver disease immediately to a hepatologist or to a gastroenterologist with an interest in hepatology. Symptoms of decompensated liver disease include (but are not limited to) ascites, encephalopathy and gastrointestinal haemorrhage.

Children and young people who are HBsAg positive

1.2.6 Arrange the following tests for children and young people who are HBsAg positive:

- HBeAg/anti-HBe status
- HBV DNA level
- anti-HBc IgM
- anti-HCV
- anti-HDV
- anti-HIV
- anti-HAV
- additional laboratory tests, including ALT or AST, GGT, serum albumin, total bilirubin, total globulins, full blood count and prothrombin time
- tests for HCC, including hepatic ultrasound and alpha-fetoprotein testing.

1.2.7 Refer all children and young people who are HBsAg positive to a paediatric hepatologist or to a gastroenterologist or infectious disease specialist with an interest in hepatology.

1.2.8 Include the results of the initial tests with the referral (see recommendation 1.2.6).

1.3 Assessment of liver disease in secondary

specialist care

Adults with chronic hepatitis B

Refer to recommendations 1.5.3 to 1.5.7 in the section on adults with chronic hepatitis B for detailed guidance on offering antiviral treatment.

1.3.1 Ensure all healthcare professionals who refer adults for non-invasive tests for liver disease are trained to interpret the results and aware of co-factors that influence liver elasticity (for example, fatty liver caused by obesity or alcohol misuse).

1.3.2 Discuss the accuracy, limitations and risks of the different tests for liver disease with the patient.

1.3.3 Offer transient elastography as the initial test for liver disease in adults newly referred for assessment.

1.3.4 Offer antiviral treatment without a liver biopsy to adults with a transient elastography score greater than or equal to 11 kPa, in line with recommendation 1.5.6 in the section on adults with chronic hepatitis B (adults with a transient elastography score greater than or equal to 11 kPa are very likely to have cirrhosis and confirmation by liver biopsy is not needed).

1.3.5 Consider liver biopsy to confirm the level of fibrosis in adults with a transient elastography score between 6 and 10 kPa (the degree of fibrosis cannot be accurately predicted in adults with a transient elastography score between 6 to 10 kPa; some people may choose to have a liver biopsy in these circumstances to confirm the extent of liver disease). Offer antiviral treatment in line with recommendations 1.5.3 to 1.5.7 in the section on adults with chronic hepatitis B.

1.3.6 Offer liver biopsy to adults with a transient elastography score less than 6 kPa if they are younger than 30 years and have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females) on 2 consecutive tests conducted 3 months apart (adults with a transient elastography score less than 6 kPa are unlikely to have significant fibrosis). Offer antiviral treatment in line with recommendations 1.5.3 to

1.5.7 in the section on adults with chronic hepatitis B.

1.3.7 Do not offer liver biopsy to adults with a transient elastography score less than 6 kPa who have normal ALT (less than 30 IU/L in males and less than 19 IU/L in females) and HBV DNA less than 2000 IU/ml as they are unlikely to have advanced liver disease or need antiviral treatment (see recommendations 1.5.3 to 1.5.7 in the section on adults with chronic hepatitis B). Adults with a transient elastography score less than 6 kPa are unlikely to have significant fibrosis.

1.3.8 Offer an annual reassessment of liver disease using transient elastography to adults who are not taking antiviral treatment.

Children and young people with chronic hepatitis B

1.3.9 Discuss the accuracy, limitations and risks of liver biopsy in determining the need for antiviral treatment with the child or young person and with parents or carers (if appropriate).

1.3.10 Consider liver biopsy to assess liver disease and the need for antiviral treatment in children and young people with HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females) on 2 consecutive tests conducted 3 months apart. Offer biopsy under a general anaesthetic to children who are too young to tolerate the procedure under a local anaesthetic.

1.4 Genotype testing

1.4.1 Do not offer genotype testing to determine initial treatment in people with chronic hepatitis B.

1.5 Antiviral treatment

Recommendations 1.5.8 to 1.5.39 do not apply to people with chronic hepatitis B who also have hepatitis C, hepatitis D or HIV.

Adults with chronic hepatitis B

1.5.1 Discuss treatment options, adverse effects and long-term prognosis with the patient before starting treatment.

1.5.2 Re-assess the person's risk of exposure to HIV before starting treatment and offer repeat testing if needed.

1.5.3 Offer antiviral treatment to adults aged 30 years and older who have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L in males and greater than or equal to 19 IU/L in females) on 2 consecutive tests conducted 3 months apart.

1.5.4 Offer antiviral treatment to adults younger than 30 years who have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L in males and greater than or equal to 19 IU/L in females) on 2 consecutive tests conducted 3 months apart if there is evidence of necroinflammation or fibrosis on liver biopsy or a transient elastography score greater than 6 kPa.

1.5.5 Offer antiviral treatment to adults who have HBV DNA greater than 20,000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L in males and greater than or equal to 19 IU/L in females) on 2 consecutive tests conducted 3 months apart regardless of age or the extent of liver disease.

1.5.6 Offer antiviral treatment to adults with cirrhosis and detectable HBV DNA, regardless of HBeAg status, HBV DNA and ALT levels.

1.5.7 Consider antiviral treatment in adults with HBV DNA greater than 2000 IU/ml and evidence of necroinflammation or fibrosis on liver biopsy.

1.5.8 Antiviral treatment should be initiated only by an appropriately qualified healthcare professional with expertise in the management of viral hepatitis. Continuation of therapy under shared-care arrangements with a GP is appropriate.

1.5.9 For antivirals recommended as options in NICE technology appraisal guidance for treating chronic hepatitis B (HBeAg-positive or HBeAg-negative) see the

guidance on:

- tenofovir disoproxil for the treatment of chronic hepatitis B (TA173, 2009)
- entecavir for the treatment of chronic hepatitis B (TA153, 2008)
- peginterferon alfa-2a for the treatment of chronic hepatitis B (TA96, 2006).

1.5.10 Telbivudine is not recommended in NICE technology appraisal guidance for the treatment of chronic hepatitis B. For full details, see the guidance on telbivudine (TA154, 2008).

1.5.11 Do not offer adefovir dipivoxil for treatment of chronic hepatitis B.

Treatment sequence in adults with HBeAg-positive chronic hepatitis B and compensated liver disease

1.5.12 Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-positive chronic hepatitis B and compensated liver disease. Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

1.5.13 Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and/or if HBsAg is greater than 20,000 IU/ml, and offer second-line treatment in line with recommendations 1.5.14 and 1.5.15.

1.5.14 Offer tenofovir disoproxil as second-line treatment to people who do not undergo HBeAg seroconversion or who relapse (revert to being HBeAg positive following seroconversion) after first-line treatment with peginterferon alfa-2a.

1.5.15 Offer entecavir as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated.

1.5.16 Review adherence in people taking tenofovir disoproxil who have detectable HBV DNA at 48 weeks of treatment and, if appropriate, provide support in line with

NICE's guideline on medicines adherence.

- If HBV DNA remains detectable at 96 weeks, and there is no history of lamivudine resistance, consider adding lamivudine to tenofovir disoproxil.
- In people with a history of lamivudine resistance, consider adding entecavir to tenofovir disoproxil.

1.5.17 Consider stopping nucleoside or nucleotide analogue treatment 12 months after HBeAg seroconversion in people without cirrhosis.

1.5.18 Do not stop nucleoside or nucleotide analogue treatment 12 months after HBeAg seroconversion in people with cirrhosis.

Treatment sequence in adults with HBeAg-negative chronic hepatitis B and compensated liver disease

1.5.19 Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-negative chronic hepatitis B and compensated liver disease. Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

1.5.20 Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and HBsAg has not decreased, and consider second-line treatment in line with recommendation 1.5.21.

1.5.21 Offer entecavir or tenofovir disoproxil as second-line treatment to people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a.

1.5.22 Consider switching from tenofovir disoproxil to entecavir, or from entecavir to tenofovir disoproxil, as third-line treatment in people who have detectable HBV DNA at 48 weeks of treatment.

1.5.23 Consider stopping nucleoside or nucleotide analogue treatment 12 months after achieving undetectable HBV DNA and HBsAg seroconversion in people without cirrhosis.

1.5.24 Do not stop nucleoside or nucleotide analogue treatment after achieving undetectable HBV DNA and HBsAg seroconversion in patients with cirrhosis.

Children and young people with chronic hepatitis B and compensated liver disease

1.5.25 Discuss treatment options, adverse effects and long-term prognosis with the child or young person and with parents or carers (if appropriate) before starting treatment.

1.5.26 Re-assess the child or young person's risk of exposure to HIV before starting treatment and offer repeat testing if necessary.

1.5.27 Offer antiviral treatment if there is evidence of significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3) or abnormal ALT (greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females) on 2 consecutive tests conducted 3 months apart.

1.5.28 Consider a 48-week course of peginterferon alfa-2a as first-line treatment in children and young people with chronic hepatitis B and compensated liver disease.Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

In June 2013, this was an off-label use of peginterferon alfa-2a in children. See NICE's information on prescribing medicines.

1.5.29 Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and/or if HBsAg is greater than 20,000 IU/ml.

1.5.30 Consider a nucleoside or nucleotide analogue as second-line treatment in children and young people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a.

In October 2017, this was an off-label use of peginterferon alfa-2a in children. See

NICE's information on prescribing medicines.

Adults with decompensated liver disease

1.5.31 Manage decompensated liver disease in adults in conjunction with a liver transplant centre.

1.5.32 Do not offer peginterferon alfa-2a to people with chronic hepatitis B and decompensated liver disease.

1.5.33 Offer entecavir as first-line treatment in people with decompensated liver disease if there is no history of lamivudine resistance.

- Offer tenofovir disoproxil to people with a history of lamivudine resistance.
- Reduce the dose of tenofovir disoproxil in people with renal impairment, in line with guidance in the summary of product characteristics.

Women who are pregnant or breastfeeding

1.5.34 Discuss with pregnant women the benefits and risks of antiviral treatment for them and their baby.

1.5.35 Offer tenofovir disoproxil to women with HBV DNA greater than 10^7 IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby.

In June 2013, this was an off-label use of tenofovir disoproxil. See NICE's information on prescribing medicines.

1.5.36 Monitor quantitative HBV DNA 2 months after starting tenofovir disoproxil and ALT monthly after the birth to detect postnatal HBV flares in the woman.

1.5.37 Stop tenofovir disoproxil 4 to 12 weeks after the birth unless the mother meets criteria for long-term treatment (see recommendations 1.5.4 to 1.5.9).

1.5.38 Offer active and passive hepatitis B immunisation in infants and follow up in line

with the guidance below:

- Department of Health and Social Care's best practice guidance on Hepatitis B antenatal screening and newborn immunisation programme
- Immunisation against infectious disease (the Green book)
- NICE's guideline on hepatitis B and C testing
- NICE's guideline on vaccine uptake in the general population.

1.5.39 Advise women that there is no risk of transmitting HBV to their babies through breastfeeding if guidance on hepatitis B immunisation has been followed, and that they may continue antiviral treatment while they are breastfeeding.

Adults who are co-infected with hepatitis C

1.5.40 Offer peginterferon alfa and ribavirin in adults co-infected with chronic hepatitis B and C. Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

Adults who are co-infected with hepatitis D

1.5.41 Offer a 48-week course of peginterferon alfa-2a in people co-infected with chronic hepatitis B and hepatitis D infection who have evidence of significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3). Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

1.5.42 Consider stopping peginterferon alfa-2a if there is no decrease in HDV RNA after 6 months to 1 year of treatment. Otherwise, continue treatment and re-evaluate treatment response annually.

1.5.43 Stop treatment after HBsAg seroconversion.

1.5.44 Bulevirtide is recommended as an option in NICE technology appraisal guidance for treating chronic hepatitis D in adults with compensated liver disease if there is evidence of significant fibrosis and their hepatitis has not responded to peginterferon alfa-2a or they cannot have interferon-based therapy. For full details, see the guidance on bulevirtide (TA896, 2023).

Prophylactic treatment during immunosuppressive therapy

In June 2013, the use of entecavir, lamivudine and tenofovir disoproxil as prophylactic treatments during immunosuppressive therapy was off-label. See NICE's information on prescribing medicines.

1.5.45 Perform the following tests in people who are HBsAg and/or anti-HBc positive before starting immunosuppressive therapy for autoimmune or atopic diseases, chemotherapy, bone marrow or solid organ transplantation:

- antibody to hepatitis B surface antigen (anti-HBs)
- plasma or serum HBV DNA level
- ALT.

1.5.46 In people who are HBsAg positive and have HBV DNA greater than 2000 IU/ml, offer prophylaxis with entecavir or tenofovir disoproxil.

- Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after HBeAg seroconversion and HBV DNA is undetectable.

1.5.47 In people who are HBsAg positive and have HBV DNA less than 2000 IU/ml, offer prophylaxis.

- Consider lamivudine if immunosuppressive therapy is expected to last less than 6 months.
  - Monitor HBV DNA monthly in people treated with lamivudine and change to tenofovir disoproxil if HBV DNA remains detectable after 3 months.

- Consider entecavir or tenofovir disoproxil if immunosuppressive therapy is expected to last longer than 6 months.
- Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy.

1.5.48 In people who are HBsAg negative and anti-HBc positive (regardless of anti-HBs status) and are starting rituximab or other B cell-depleting therapies:

- offer prophylaxis with lamivudine
- start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy.

1.5.49 In people who are HBsAg negative, anti-HBc positive and anti-HBs negative and are not taking rituximab or other B cell-depleting therapies:

- monitor HBV DNA monthly and offer prophylaxis to people whose HBV DNA becomes detectable
  - consider lamivudine in people with HBV DNA less than 2000 IU/ml and for whom immunosuppressive therapy is expected to last less than 6 months; change to tenofovir disoproxil if HBV DNA remains detectable after 6 months
  - consider entecavir or tenofovir disoproxil in people with HBV DNA greater than 2000 IU/ml and for whom immunosuppressive therapy is expected to last longer than 6 months
  - continue antiviral therapy for a minimum of 6 months after stopping immunosuppressive therapy.

1.5.50 Do not offer prophylaxis to people who are HBsAg negative and anti-HBc and anti-HBs positive who are not taking rituximab or other B cell-depleting therapies.

1.6 Monitoring

Monitoring in people who do not meet criteria for antiviral

treatment

Further information on the progression of chronic hepatitis B can be found in the context section.

Adults with HBeAg-positive disease in the immune-tolerant and immune clearance phases

1.6.1 Monitor ALT levels every 24 weeks in adults with HBeAg-positive disease who are in the immune-tolerant phase (defined by active viral replication and normal ALT levels [less than 30 IU/L in males and less than 19 IU/L in females]).

1.6.2 Monitor ALT every 12 weeks on at least 3 consecutive occasions if there is an increase in ALT levels.

Adults with inactive chronic hepatitis B (immune-control phase)

1.6.3 Monitor ALT and HBV DNA levels every 48 weeks in adults with inactive chronic hepatitis B infection (defined as HBeAg negative on 2 consecutive tests with normal ALT [less than 30 IU/L in males and less than 19 IU/L in females] and HBV DNA less than 2000 IU/ml).

- Consider monitoring more frequently (for example, every 12–24 weeks) in people with cirrhosis who have undetectable HBV DNA.

Children and young people

1.6.4 Monitor ALT levels every 24 weeks in children and young people with HBeAg-positive disease who have normal ALT levels (less than 30 IU/L for males and less than 19 IU/L for females) and no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3).

1.6.5 Review annually children and young people with HBeAg-negative disease who have normal ALT (less than 30 IU/L for males and less than 19 IU/L for females), no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3) and HBV DNA less than 2000 IU/ml.

1.6.6 Review every 12 weeks children and young people with HBeAg-negative disease who have abnormal ALT (greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females) and HBV DNA greater than 2000 IU/ml.

Children, young people and adults with HBeAg or HBsAg seroconversion after antiviral treatment

1.6.7 In people with HBeAg seroconversion after antiviral treatment, monitor HBeAg, anti-HBe, HBV DNA level and liver function at 4, 12 and 24 weeks after HBeAg seroconversion and then every 6 months.

1.6.8 Monitor HBsAg and anti-HBs annually in people with HBsAg seroconversion after antiviral treatment and discharge people who are anti-HBs positive on 2 consecutive tests.

Monitoring in people taking antiviral treatment

Children, young people and adults taking peginterferon alfa-2a

In October 2017, the use of peginterferon alfa-2a as an antiviral treatment in children with chronic hepatitis B was off-label. See NICE's information on prescribing medicines.

1.6.9 Review injection technique and adverse effects weekly during the first month of treatment in people taking peginterferon alfa-2a.

1.6.10 Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels) and thyroid function (and in children, weight and height) before starting peginterferon alfa-2a and 2, 4, 12, 24, 36 and 48 weeks after starting treatment to detect adverse effects.

1.6.11 Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting peginterferon alfa-2a at 12, 24 and 48 weeks after starting treatment to

determine treatment response.

Children, young people and adults with compensated liver disease taking entecavir or lamivudine

In October 2017, the use of entecavir in children younger than 2 years with chronic hepatitis B and compensated liver disease was off-label. See NICE's information on prescribing medicines.

1.6.12 Monitor full blood count, liver function (including bilirubin, albumin and ALT) and renal function (including urea and electrolyte levels) in people with compensated liver disease before starting entecavir or lamivudine, 4 weeks after starting treatment and then every 3 months to detect adverse effects.

1.6.13 Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting entecavir or lamivudine, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence.

1.6.14 Monitor HBV DNA levels every 12 weeks in people with HBeAg-negative disease who have been taking lamivudine for 5 years or longer.

Children, young people and adults with compensated liver disease taking tenofovir disoproxil

In October 2017, the use of tenofovir disoproxil in children younger than 12 years with chronic hepatitis B and compensated liver disease was off-label. See NICE's information on prescribing medicines.

1.6.15 Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio), and phosphate levels in people with compensated liver disease before starting tenofovir disoproxil, 4 weeks after starting treatment and then every 3 months to

detect adverse effects.

1.6.16 Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting tenofovir disoproxil, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence.

Children, young people and adults with decompensated liver disease who are taking entecavir or lamivudine

1.6.17 Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio), blood clotting, HBV DNA level and HBeAg status in people with decompensated liver disease before starting entecavir or lamivudine and weekly after starting treatment to assess treatment response and adverse effects. When the person is no longer decompensated, follow the recommendations in the section on children, young people and adults with compensated liver disease taking entecavir or lamivudine.

In October 2017, the use of entecavir in children younger than 2 years was off-label. See NICE's information on prescribing medicines..

Children, young people and adults with decompensated liver disease who are taking tenofovir disoproxil

1.6.18 Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio) and phosphate, blood clotting, HBV DNA level and HBeAg status in people with decompensated liver disease before starting tenofovir disoproxil and weekly after starting treatment to assess treatment response and adverse effects. When the person is no longer decompensated, follow the recommendations in the section on children, young people and adults with compensated liver disease taking tenofovir disoproxil'.

In October 2017, the use of entecavir in children younger than 2 years was off-label. See NICE's information on prescribing medicines.

1.7 Surveillance testing for hepatocellular carcinoma in adults with chronic hepatitis B

1.7.1 Perform 6-monthly surveillance for HCC by hepatic ultrasound and alpha-fetoprotein testing in people with significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3) or cirrhosis.

1.7.2 In people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3), consider 6-monthly surveillance for HCC if the person is older than 40 years and has a family history of HCC and HBV DNA greater than or equal to 20,000 IU/ml.

1.7.3 Do not offer surveillance for HCC in people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3) who have HBV DNA less than 20,000 IU/ml and are younger than 40 years.

Terms used in this guidance

Chronic hepatitis B

Chronic hepatitis B is defined as persistence of hepatitis B surface antigen (HBsAg) for 6 months or more after acute infection with hepatitis B virus (HBV).

HBV DNA

HBV DNA level, or 'viral load', is an indicator of viral replication. Higher HBV DNA levels are usually associated with an increased risk of liver disease and hepatocellular carcinoma. HBV DNA level typically falls in response to effective antiviral treatment.

Hepatitis B surface antigen (HBsAg)

Hepatitis B surface antigen (HBsAg) is a viral protein detectable in the blood in acute and chronic hepatitis B infection.

HBsAg seroconversion

The development of antibodies against HBsAg is known as HBsAg seroconversion. It signifies clearance of HBsAg and resolution of the chronic infection.

Hepatitis B e antigen (HBeAg)

Hepatitis B e antigen (HBeAg) is an indicator of viral replication, although some variant forms of the virus do not express HBeAg (see HBeAg-negative chronic hepatitis B in this section). Active infection can be described as HBeAg-positive or HBeAg-negative according to whether HBeAg is secreted.

HBeAg-negative chronic hepatitis B

HBeAg-negative hepatitis B is a form of the virus that does not cause infected cells to secrete HBeAg. People can be infected with the HBeAg-negative form of the virus from the beginning, or the viral mutation can emerge later in the course of infection in people initially infected with the HBeAg-positive form of the virus.

HBeAg seroconversion

HBeAg seroconversion occurs when people infected with the HBeAg-positive form of the virus develop antibodies against the 'e' antigen. The seroconverted disease state is referred to as the 'inactive HBV carrier state' when HBeAg has been cleared, anti-HBe is present and HBV DNA is undetectable or less than 2000 IU/ml. Once seroconversion has taken place, most people remain in the inactive HBV carrier state (the immune-control phase; see the information about the natural history of chronic HBV infection in the context section). However, increasing HBV DNA and recurrent hepatitis after seroconversion indicate the emergence of the HBeAg-negative strain of the virus (the immune-escape phase; see the information about the natural history of chronic HBV infection in the context section).

Recommendations for research

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

1 Stopping antiviral treatment in HBeAg-negative disease

Further research should be undertaken to evaluate the clinical and cost effectiveness of hepatitis B surface antigen (HBsAg) quantitative assays in determining treatment duration in hepatitis B e antigen- (HBeAg) negative disease.

Why this is important

In HBeAg-positive disease, HBeAg seroconversion is a predictor of durable response to antiviral treatment and can be used as a milestone after which treatment can be stopped. At present, similar parameters have not been defined in HBeA'g-negative disease. Quantitative HBsAg may have a role in determining treatment duration in this setting. Establishing threshold levels for HBsAg titre associated with durable off-treatment control in HBeAg-negative disease would transform current treatment strategies. People on long-term nucleoside or nucleotide analogues could safely stop treatment once they achieved a threshold level of HBsAg. Further research is needed to define these levels of HBsAg and to determine when treatment in HBeAg-negative disease can be safely stopped.

2 ALT values for children and young people

Further research should be undertaken to examine whether the upper limit of normal ALT values for adults (below 30 IU/L for males and below 19 IU/L for females) are appropriate for use in children and young people with chronic hepatitis B when making decisions on when to initiate treatment.

Why this is important

Recent studies have highlighted the imprecision of using biochemical activity as a measure of immune activity in children and young people with chronic hepatitis B. Researchers have

found T-cell exhaustion and even HBV-specific immune responses in children and young people considered to have immune-tolerant disease. These findings need to be validated in larger studies to see if upper limit of normal ALT values derived from adults accurately reflect disease activity in children and young people. Further research is needed to investigate whether there is a genuine state of immune tolerance in children and young people reflected in lower levels of biochemical activity and a lower upper limit of normal ALT value.

3 Long-term safety of tenofovir disoproxil in chronic hepatitis B

Further research should be undertaken to determine the long-term safety of tenofovir disoproxil, including the risk of clinically significant hypophosphataemia and related bone toxicity, in people with chronic hepatitis B. The cost effectiveness of routine monitoring for phosphate loss and bone disease in people with chronic hepatitis B who are receiving tenofovir disoproxil treatment needs further evaluation.

Why this is important

Tenofovir disoproxil is recommended as an option for treatment of people with chronic hepatitis B, and is typically prescribed for long-term use. Kidney dysfunction has been reported in people treated with tenofovir disoproxil, including rare cases of proximal renal tubular dysfunction that appear related to long-term exposure but are not well understood. Adverse renal effects such as hypophosphataemia may have an impact on bone architecture which could result in clinical problems such as fragility fractures. Monitoring for phosphate loss and bone disease could have a role in preventing clinically significant bone problems in people with chronic hepatitis B receiving long-term tenofovir disoproxil. However, the cost effectiveness and clinical utility of routine monitoring needs to be established before recommendations can be made about its use.

4 Prophylactic treatment in people receiving immunosuppressive therapy

Further research should be undertaken to determine whether long-term use of mild immunosuppressive agents for autoimmune and allergic problems presents a risk for reactivation of HBV infection in people with previous or current chronic hepatitis B,

including occult HBV infection. The cost effectiveness of routine tests for HBV in this population, including HBV DNA for occult HBV infection, and the need for prophylactic treatment with nucleoside or nucleotide analogues needs further evaluation.

Why this is important

Reactivation of HBV may occur spontaneously or arise during immunosuppression. Solid organ transplantation, chemotherapy and immunosuppressive drugs used to treat autoimmune diseases are key causes of HBV reactivation. Antiviral agents can be used as prophylaxis to prevent reactivation of HBV infection in people receiving immunosuppressive therapy but the optimal treatment and duration of therapy are unknown. Decision-making and cost-effectiveness studies are needed to determine optimal screening strategies to identify people at risk of HBV reactivation. People with occult HBV (including people coming from high endemicity regions) might carry a low, but not negligible, risk of viral reactivation. Prospective studies are needed to assess the risk of HBV reactivation in people receiving mild immunosuppressants or biological treatment for autoimmune diseases, to identify risk factors that predict HBV reactivation in this population, and evaluate treatment or pre-emptive strategies using existing nucleoside and nucleotide analogues.

Context

Chronic hepatitis B describes a spectrum of disease usually characterised by the presence of detectable hepatitis B surface antigen (HBsAg) in the blood or serum for longer than 6 months. In some people, chronic hepatitis B is inactive and does not present significant health problems, but others may progress to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). The progression of liver disease is associated with hepatitis B virus (HBV) DNA levels in the blood. Without antiviral treatment, the 5-year cumulative incidence of cirrhosis ranges from 8 to 20%. People with cirrhosis face a significant risk of decompensated liver disease if they remain untreated. Five-year survival rates among people with untreated decompensated cirrhosis can be as low as 15%. Chronic hepatitis B can be divided into e antigen- (HBeAg) positive or HBeAg-negative disease based on the presence or absence of e antigen. The presence of HBeAg is typically associated with higher rates of viral replication and therefore increased infectivity.

The goal of treatment for chronic hepatitis B is to prevent cirrhosis, HCC and liver failure. In clinical practice surrogate markers are used to monitor progression of disease and treatment response, and include normalisation of serum alanine aminotransferase (ALT) levels, decrease in inflammation scores with no worsening or improvement in fibrosis on liver biopsies, suppression of serum HBV DNA to undetectable levels, loss of HBeAg and seroconversion to HBe antibody (anti-HBe), and loss of HBsAg and seroconversion to HBs antibody (anti-HBs).

Antiviral therapy suppresses HBV replication and decreases hepatic inflammation and fibrosis, thereby reducing the likelihood of serious clinical disease. Since the introduction of effective treatment in the form of interferon alfa, several nucleoside and nucleotide analogues are now approved for use in adults with chronic hepatitis B, together with a pegylated form of interferon alfa. With multiple treatment options that are efficacious and safe, the key questions are which patients need immediate treatment and what sequence and combination of drug regimens should be used, and which patients can be monitored and delay treatment.

In this guideline we cover the following:

- information needs of people with chronic hepatitis B and their carers
- where children, young people and adults with chronic hepatitis B should be assessed

- assessment of liver disease, including the use of non-invasive tests and genotype testing
- criteria for offering antiviral treatment
- the efficacy, safety and cost effectiveness of currently available treatments
- selection of first-line therapy
- management of treatment failure or drug resistance
- whether there is a role for combination therapy
- when it is possible to stop treatment
- managing the care of pregnant and breastfeeding women and prevention of vertical transmission
- prophylactic treatment during immunosuppressive therapy
- monitoring for treatment response, severity of fibrosis and development of HCC.

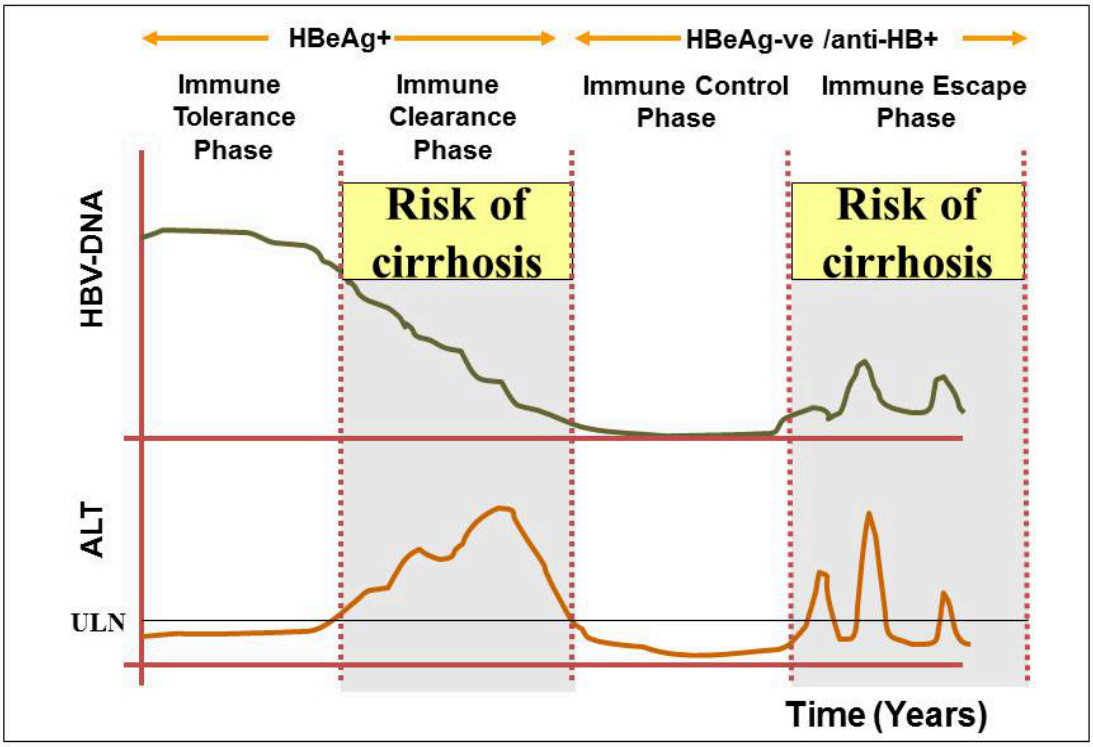
The spontaneous mutation rate of HBV DNA is high. Exposure of HBV to nucleoside or nucleotide analogues selects for mutations in the polymerase gene that confer resistance or decreased susceptibility to the drugs. The relative risk of drug resistance must be taken into account when considering treatment with nucleoside or nucleotide analogues, including the level of cross resistance between different agents.

Figure 1 depicts the natural history of chronic HBV infection. The immune-tolerance phase is seen in HBeAg-positive disease and is characterised by high levels of HBV replication with normal ALT levels and limited liver necroinflammation. Because there is minimal immune response to the virus it is unusual for spontaneous HBeAg loss to occur. This phase is commonly seen in children. It is followed by an immune-clearance or immune-reactive phase in which the immune system recognises and starts to clear the virus. ALT levels are typically elevated or fluctuating, and there is a higher risk of liver fibrosis. This tends to be the initial phase in people infected with HBV as adults. It lasts from weeks to years and ends with HBeAg seroconversion.

With the loss of HBeAg the person may enter an immune-control phase with very low or undetectable HBV DNA levels, normal ALT and minimal fibrosis progression. However, some people may experience rising HBV DNA levels despite HBeAg negativity. This is caused by virions that do not express HBeAg because of genetic mutations. This immune-

escape phase can lead to active necroinflammation and progression of fibrosis.

Figure 1. Natural history of chronic HBV infection



After Chu et al, Hepatology 1985;5:431-34 ULN: upper limit of normal of ALT

Substantial progress has been made in the treatment of chronic hepatitis B in the past decade but the appropriate time for starting treatment remains a topic of debate. Although currently available treatment is effective in suppressing HBV replication, it fails to eradicate the virus necessitating long treatment duration and perhaps lifelong treatment.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the General Medical Council's good practice in prescribing and managing medicines and devices for further information. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are noted in the recommendations.

Finding more information and committee details

To find out what NICE has said on topics related to this guideline, see the NICE topic page on hepatitis.

For full details of the evidence and the guideline's committee's discussions, see the full guideline. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put NICE guidance into practice.

Update information

October 2017: We have updated the information on the off-label use of entecavir in the sections on children, young people and adults with compensated liver disease and decompensated liver disease who are taking entecavir or lamivudine.

January 2014: A correction has been made to the units used for ALT in men and women. The abnormal ALT levels should read greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females, not IU/ml. This has been changed in the relevant recommendations and recommendation for research 2.

June 2013: Recommendations in this guideline update and replace recommendations 1.2 to 1.4 in adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96). NICE technology appraisal guidance 153, 154, 173 and recommendation 1.1 of NICE technology appraisal guidance 96 have been incorporated into this guideline.

Minor changes since publication

September 2024: We added links to relevant technology appraisal guidance in the section on antiviral treatment.

ISBN: 978-1-4731-4724-9