Appendix A: Summary of evidence from surveillance

4 year surveillance (2017) – Hepatitis B (chronic) (2013) NICE guideline CG165

Summary of evidence from surveillance

Patient information

Q – 01 What information do patients with CHB and their carers need about the benefits and risks of treatment options?

Recommendations derived from this review question

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 Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (NICE public health guidance 43).

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 Patient experience in adult NHS services (NICE clinical guidance 138).

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Assessment and referral in primary care

Q – 02 What is the most appropriate healthcare setting to initiate relevant diagnostic tests (for example, Liver Function Tests, HBeAg, quantitative HBsAg, quantitative HBV DNA, anti HCV, anti HDV, anti HIV) in people who are HBsAg positive?

Recommendations derived from this review question

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 delta 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

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of receiving the screening test result and to allow treatment in the third trimester (see recommendation 1.5.39).

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).

Surveillance decision

This review question should not be updated.

4-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

A topic expert noted that access to the HBsAg test remained inadequate with variation in access across the NHS. This test is used to detect, and help diagnose, acute and chronic HBV infections.

Impact statement

No relevant evidence was identified to support the topic expert feedback and thus no impact on the recommendations is anticipated.

New evidence is unlikely to change guideline recommendations.

Assessment of liver disease in secondary specialist care

Q – 03 What is the diagnostic accuracy of non-invasive methods (e.g. transient elastography, serum fibrosis markers, aspartate aminotransferase/ platelet

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ratio index, magnetic resonance spectroscopy) to assess severity of necro-inflammatory activity and liver fibrosis?

Recommendations derived from this review question

Adults with chronic hepatitis B

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[4], in line with recommendation 1.5.6.

1.3.5 Consider liver biopsy to confirm the level of fibrosis in adults with a transient elastography score between 6 and 10 kPa[5]. Offer antiviral treatment in line with recommendations 1.5.3 to 1.5.7.

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 [6]. Offer antiviral treatment in line with recommendations 1.5.3 to 1.5.7.

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). [6]

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.

Footnotes

[4] 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.

[5] 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.

[6] Adults with a transient elastography score less than 6 kPa are unlikely to have significant fibrosis.

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Surveillance decision

This review question should not be updated.

4-year surveillance summary

Transient elastography

Two systematic reviews were identified that explored the use of transient elastography to determine fibrosis and cirrhosis staging in people with chronic HBV infection. The first review (Li (2016), n=27 studies) assessed transient elastography compared to liver biopsy. The summary sensitivity for F > 2, F > 3 and F = 4 was 0.81 (0.76 to 0.85), 0.82 (0.75 to 0.87) and 0.86 (0.82 to 0.90), respectively, and the summary specificity was 0.82 (0.76 to 0.87), 0.87 (0.82 to 0.90) and 0.88 (0.84 to 0.90), respectively. The corresponding area under the summary receiver operating characteristic (ROC) curve was 0.88 (0.85 to 0.91), 0.91 (0.88 to 0.93) and 0.93 (0.91 to 0.95), respectively. The review reported that transient elastography showed good accuracy when compared to liver biopsy in diagnosing liver fibrosis in patients with HBV. The second review (Xu (2015), n= 19 studies) reported summary ROC for transient elastography for diagnosing significant fibrosis and cirrhosis as 0.823 and 0.911 respectively. The pooled diagnostic odds ratios (DOR) for transient elastography for diagnosing significant fibrosis and cirrhosis were 11.19 (6.63 to 18.89) and 26.87 (17.88 to 40.38), respectively. The review reported that liver stiffness measurement using transient elastography showed good diagnostic accuracy when compared to liver biopsy for significant fibrosis and cirrhosis.

FIB-4 index

Two systematic reviews (Li (2014), n=22 studies and Yin (2017), n=26 studies) were identified which assessed the accuracy of the FIB-4 index compared to liver biopsy in the diagnosis of HBV related fibrosis and cirrhosis in people with chronic HBV infection. Li et al (2014) reported that for significant fibrosis, the area under the hierarchical summary receiver operating curve (AUHSROC) was 0.78 (0.74 to 0.81). The recommended cut off value was between 1.45 and 1.62, and the AUHSROC, summary sensitivity and specificity were 0.78 (0.74 to 0.81), 0.65 (0.56 to 0.73) and 0.77 (0.7 to 0.83), respectively. For cirrhosis, the AUHSROC was 0.89 (0.85 to 0.91). The recommended cut off value was between 2.9 and 3.6. The AUHSROC, summary sensitivity and specificity were 0.96 (0.92 to 1.00), 0.42 (0.36 to 0.48) and 0.96 (0.95-0.97). The review stated the FIB-4 index can detect significant fibrosis and cirrhosis in people with chronic HBV infection, but showed suboptimal accuracy in excluding fibrosis and cirrhosis.

Yin et al (2017) reported pooled parameters calculated from all the included studies with a sensitivity of 0.69 (0.63 to 0.75), specificity of 0.81 (0.73 to 0.87), Positive likelihood ratio (PLR) of 3.63 (2.66 to 4.94), Negative-likelihood ratio (NLR) of 0.38 (0.32 to 0.44), DOR of 9.57 (6.67 to 13.74), and area under the curve (AUC) of 0.80 (0.76 to 0.83). Results from a subgroup analysis showed that choice of cut-off was the source of heterogeneity. The sensitivity and specificity when using a cut-off >2 was 0.69 and 0.95 with the AUC of 0.90 (0.87 to 0.92). The review indicated that the overall diagnostic value of FIB-4 was not very high for liver fibrosis in patients with HBV but showed good diagnostic value for detecting liver fibrosis compared to liver biopsy when the diagnostic threshold value was more than 2.0.

FibroTest

New evidence from a systematic review (Salkic (2014), n=29 studies) was identified which assessed the accuracy of the FibroTest (FT) versus liver biopsy in the diagnosis of HBV related fibrosis and cirrhosis in people with chronic HBV infection. The AUHSROC for significant liver fibrosis and for all included studies was 0.84 (0.78 to 0.88). At the FT threshold of 0.48, the sensitivity, specificity, and DOR of FT for significant fibrosis were 61 (48 to 72%), 80 (72 to 86%), and 6.2% (3.3 to 11.9), respectively for liver cirrhosis and for all included studies was 0.87 (0.85 to 0.90). At the FT threshold of 0.74, the sensitivity, specificity, and DOR of FT for cirrhosis was 62 (47 to 75%), 91 (88 to 93%), and 15.7% (8.6 to 28.8), respectively. The review reported that the FT is of value in the exclusion of patients with

chronic HBV-related cirrhosis, but has suboptimal accuracy in the detection of significant (not defined in study abstract) fibrosis and cirrhosis.

FibroScan

A systematic review (Wang (2015), n=15 studies) was identified which determined the diagnostic value of FibroScan for the staging of liver fibrosis in people with chronic HBV infection. Pooled sensitivity, 0.77 (0.69 to 0.83), specificity 0.84 (0.70 to 0.87), PLR, 3.8 (2.6 to 5.6), NLR, 0.29 (0.22 to 0.38), DOR, 13 (8 to 21), and the AUC of ROC were 0.82 (0.82 to 0.88) for hepatic fibrosis. For early hepatic cirrhosis they were 0.81 (0.73 to 0.87), 0.89 (0.86 to 0.92), 7.5 (5.3 to 10.3), 0.21 (0.14 to 0.31), 36 (20 to 65), 0.93 (0.90 to 0.95). The review reported FibroScan as accurate in the diagnosis of early hepatic fibrosis but not for hepatic cirrhosis in people with chronic HBV infection.

Topic expert feedback

A topic expert noted that both systematic reviews reported looking at transient elastography used fibroscan, either solely or mostly within them.

Impact statement

New evidence indicates transient elastography as showing good diagnostic accuracy in diagnosing both fibrosis and cirrhosis when compared to the reference standard of liver biopsy whereas the use of the FIB-4 index, FibroScan or Fibrotest did not indicate sufficient accuracy in people with chronic HBV infection. Transient elastography is currently recommended for use within the guideline (recommendations 1.3.3 & 1.3.8) and the outlined new evidence would support this.

New evidence is unlikely to change guideline recommendations.

Genotype testing

Q – 04 What is the clinical and cost-effectiveness of genotypic testing in determining whether to offer antiviral treatment in people with CHB?

Recommendations derived from this review question

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

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Antiviral treatment

Q – 05 **What are the thresholds (e.g. HBV DNA, ALT levels) for starting treatment after initial diagnosis and pre-therapeutic tests of CHB?**

Q – 06 **In people with CHB, what is the clinical and cost effectiveness of pharmacological monotherapies and combinations in achieving remission of the activity of CHB?**

Q – 07 **In people with CHB, what is the clinical and cost-effectiveness of sequential drug therapy (add-on or switching monotherapies) in achieving remission of the activity of CHB?**

Q – 08 **In chronic hepatitis B infected people with cirrhosis, including those with liver decompensation, what is the clinical and cost effectiveness of antiviral treatment to prevent decompensation and/or liver transplantation?**

Q – 09 **In pregnant/lactating women with chronic hepatitis B what is the clinical and cost-effectiveness of anti-viral therapy in order to reduce risk of vertical transmission from mother to infant?**

Q – 10 **In people who are immunocompromised, what is the clinical and cost effectiveness of prophylactic treatment in reducing risk of hepatitis B virus reactivation and severity of flares?**

Recommendations derived from these review questions

Adults with chronic hepatitis B

Recommendations 1.5.8 to 1.5.12 are reproduced from existing NICE technology appraisals on options for the treatment of chronic hepatitis B, and 1.5.13 to 1.5.15 update guidance in NICE technology appraisal 96[7]. The GDG has reviewed the evidence and has made recommendations on treatment sequences and combination drug regimens (see recommendations 1.5.16 to 1.5.28). Recommendations 1.5.8 to 1.5.43 do not apply to people with chronic hepatitis B who also have hepatitis C, hepatitis D or HIV.

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

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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 Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications. [This recommendation is from Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96).]

1.5.9 Entecavir, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated. [This recommendation is from Entecavir for the treatment of chronic hepatitis B (NICE technology appraisal guidance 153).]

1.5.10 Tenofovir disoproxil, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated. [This recommendation is from Tenofovir disoproxil fumarate for the treatment of hepatitis B (NICE technology appraisal guidance 173).]

1.5.11 Telbivudine is not recommended for the treatment of chronic hepatitis B. [This recommendation is from Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154).]

1.5.12 People currently receiving telbivudine should have the option to continue therapy until they and their clinicians consider it appropriate to stop. [This recommendation is from Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154).]

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

1.5.14 People currently receiving adefovir dipivoxil should be offered the option to switch to a different treatment. Offer tenofovir disoproxil or entecavir, depending on previous antiviral exposure:

- offer tenofovir disoproxil to people with a history of lamivudine resistance.

1.5.15 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.

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

1.5.16 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 [8].

1.5.17 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 1.5.18 and 1.5.19.

1.5.18 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.

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

1.5.20 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 Medicines adherence (NICE clinical guidance 76).

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

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- In people with a history of lamivudine resistance, consider adding entecavir to tenofovir disoproxil.

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

1.5.22 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

1.5.23 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 [8].

1.5.24 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 1.5.25.

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

1.5.26 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.

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

1.5.28 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

1.5.29 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.

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

1.5.31 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.

1.5.32 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 [8],[9].

1.5.33 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.

1.5.34 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 [10].

Adults with decompensated liver disease

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

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

1.5.37 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.

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Women who are pregnant or breastfeeding

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

1.5.39 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 [11].

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

1.5.41 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 1.5.8).

1.5.42 Offer active and passive hepatitis B immunisation in infants and follow up in line with the guidance below:

- Hepatitis B antenatal screening and newborn immunisation programme: best practice guidance.
- Immunisation against infectious disease (the Green book).
- Hepatitis B and C: ways to promote and offer testing. NICE public health guidance 43 (2012).
- Reducing differences in the uptake of immunisations. NICE public health guidance 21 (2009).

1.5.43 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

1.5.44 Offer peginterferon alfa and ribavirin in adults co-infected with chronic hepatitis B and C [8].

Adults who are co-infected with hepatitis D

1.5.45 Offer a 48-week course of peginterferon alfa-2a in people co-infected with chronic hepatitis B and hepatitis delta infection who have evidence of significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3)[8].

1.5.46 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.

1.5.47 Stop treatment after HBsAg seroconversion.

Prophylactic treatment during immunosuppressive therapy

1.5.48 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.

1.5.49 In people who are HBsAg positive and have HBV DNA greater than 2000 IU/ml, offer prophylaxis with entecavir or tenofovir disoproxil[12].

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

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

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- Consider lamivudine [12] 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[12] 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.

1.5.51 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[12].
- start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy.

1.5.52 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[12] 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[12] 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.

1.5.53 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.

Footnotes

[7] Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96), Entecavir for the treatment of chronic hepatitis B (NICE technology appraisal guidance 153), Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154) and Tenofovir disoproxil fumarate for the treatment of hepatitis B (NICE technology appraisal guidance 173).

[8] Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

[9] At the time of publication (June 2013), peginterferon alfa-2a did not have a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[10] At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

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[11] At the time of publication (June 2013), tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[12] At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Surveillance decision

This review question should not be updated.

4-year surveillance summary

Adults with chronic hepatitis B

Tenofovir disoproxil

New evidence from 10 relevant studies (7 RCTs (Buti (2016), Cai (2016), Chan (2016), Fung (2016), Lok (2012), Marcellin (2016), Murray (2012) and 3 systematic reviews (Govan (2015), Kew (2014), Wang (2015)) was identified evaluating the effectiveness of tenofovir disproxil in people with chronic (HBV) infection. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA173: Tenofovir disoproxil for the treatment of chronic hepatitis B. This information will be passed onto the technology appraisal team for consideration when the topic undergoes their review process. Two of the studies compared tenofovir disoproxil with tenofovir alafenamide suggesting non-inferiority (Chan (2016), Buti (2016)).

Telbivudine

Evidence from 12 relevant studies (5 RCTs (Chan (2012), Lou (2017), Marcellin (2015), Shen (2016), Sun (2014) and 7 systematic reviews (Dai (2015), Jiang (2013), Liang (2013 and 2016), Su (2012), Wang (2012), Zhang (2014)) was identified evaluating the effectiveness of telbivudine in people with chronic HBV infection. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA154: Telbivudine for the treatment of chronic hepatitis B. This information will be passed onto the technology appraisal team for consideration when the topic undergoes their review process.

Entecavir

New evidence from 11 relevant studies (5 RCTs (Shi (2016), Brouwer (2015), Jun (2013), Lim (2012), Xie (2014) and 6 systematic reviews (Gong (2014), Li (2015), Qi (2013), Xie (2015), Ye (2013) Zhou (2016)) was identified evaluating the effectiveness of entecavir in people with chronic HBV infection. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA153: Entecavir for the treatment of chronic hepatitis B. This information will be passed onto the technology appraisal team for consideration when the topic undergoes their review process.

Adefovir and or peginterferon alfa-2a

Evidence from 8 relevant studies (6 RCTs (Chen (2014), Ghany (2012), Bourliere (2017), Hayashi (2012), Liu (2014), Wang (2012) and 2 systematic reviews (Chen (2016) and Zhang (2016)) was identified evaluating the effectiveness of adefovir and or peginterferon alfa-2a in people with chronic HBV infection. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA96: Adefovir dipivoxil and peginterferon alfa-2 for the treatment of chronic hepatitis B. This information will be passed onto the technology appraisal team for consideration when the topic undergoes their review process.

Antiviral with interferon combination therapy vs antiviral monotherapy

New evidence from a systematic review (Wei (2015), n=17 studies) was identified evaluating antiviral treatment with interferon combination therapy versus antiviral monotherapy in people

with chronic HBV infection. Combination therapy showed better efficacy in terms of HBeAg loss, HBV-DNA undetectable rate, HBeAg seroconversion, and HBsAg loss, compared to the monotherapy group at the end of treatment (no time point specified); however, there was no significant difference in HBsAg seroconversion between the 2 regimens.

Antiviral therapy vs no therapy

A systematic review (Xie (2013), n=11 studies) was identified evaluating antiviral treatment compared to no therapy in people with chronic HBV associated liver failure. Antiviral therapy showed improved 12 month survival rates along with a significant reduction in both HBV DNA and HBeAg levels at 3 months post initiation of the treatment.

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

Evidence from a systematic review (Jonas (2016), n=14 studies) was identified evaluating antiviral therapy versus no therapy in children (<18 years) with chronic HBV infection. The use of antiviral therapy improved HBV DNA suppression, frequency of alanine aminotransferase normalisation and HBeAg seroconversion when compared to no antiviral therapy measured at posttreatment follow-up <12 months.

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

New evidence from an RCT (Heo (2012), n=72) was identified evaluating the effectiveness of switching from lamivudine to entecavir compared to continued lamivudine monotherapy in people with HBeAg-positive chronic HBV infection. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA153: Entecavir for the treatment of chronic hepatitis B. This information will be passed onto the technology appraisal team for consideration when the topic undergoes their review process.

Prophylactic treatment during immunosuppressive therapy

Evidence from a systematic review (Yang (2016), n=8 studies) was identified evaluating the effectiveness of prophylactic treatment with entecavir or lamivudine in people with chronic or resolved hepatitis B infection who were undergoing chemotherapy or immunosuppressive therapy. The review reported that entecavir is more effective than lamivudine for preventing HBV reactivation and HBV related hepatitis and that both drugs are associated with a similar risk of all-cause mortality.

Women who are pregnant or breastfeeding

Tenofovir disoproxil

Three relevant studies (2 RCTs (Pan (2016), Jourdain (2016) and a systematic review (Brown (2016)) were identified evaluating the effectiveness of tenofovir disoproxil in reducing the risk of vertical transmission in pregnant women with chronic HBV infection. Transmission rates from mother to child were reduced in those who received antiviral therapy compared to those who received no therapy when antivirals were given during the third trimester. HBV suppression was also reported in the antiviral therapy groups. The use of tenofovir disoproxil was reported as safe for use in pregnancy with no increase in adverse maternal or foetal outcome when compared to no therapy groups.

Telbivudine

New evidence from a systematic review (Lu (2014), n=7 studies) was identified evaluating the effectiveness of telbivudine in reducing the risk of vertical transmission in pregnant women with chronic HBV infection. Transmission rates were reduced in the telbivudine group compared to the no treatment group indicating that antiviral therapy with tebivudine was effective in preventing intrauterine transmission of HBV.

Lamivudine

New evidence from an RCT (Yang 2017), n=40) indicated that lamivudine was not significantly more effective in reducing the vertical transmission of HBV compared to placebo in pregnant women with chronic (HBV) infection. However, lamivudine treatment did result in a decrease in the HBV DNA load when

compared to placebo but no significant difference in vertical transmission was reported between the two groups.

Topic Expert feedback

Several studies were referenced by the topic experts as being of possible importance to the guideline. One was included from the evidence search (Marcellin 2016) and forms part of the tenofovir disoproxil treatment in adults evidence summary. A longitudinal cohort study (Buti (2015), n= 437) reported that long term treatment with tenofovir disoproxil fumarate (336 weeks) resulted in sustained HBV DNA suppression, alanine aminotransferase normalisation and HBeAg and HBsAg loss at Year 7 with no significant change in bone mineral density (Year 4 to Year 7).This study directly attempted to address research recommendation 2.3 in the guideline Although the study showed good long term safety for tenofovir disproxil, it did not address the cost effectiveness elements of the research recommendation. As such the results would not impact on the current recommendations.

Topic experts also highlighted that there is new evidence (Chan (2016), Buti (2016)) on tenofovir alafenamide, a new form of tenofovir. However, through the surveillance process it was determined that tenofovir alafenamide is not available in the UK at present although it has a marketing authorisation. As such, no impact on the guideline is currently anticipated.

Other studies highlighted by the topic experts were reviewed but were not included as they did not fit within the scope of the review questions.

Impact statement

New evidence regarding the use, within their current market authorisation, of tenofovir disoproxil, telbivudine, entecavir, adefovir dipivoxil and peginterferon alfa-2 antivirals for the treatment of HBV in adults and children, including their prophylactic use during immunosuppressive therapy, supports current recommendations within the guideline. The Yang (2016) review looked at 8 studies containing 593 patients. From an assessment of the abstract, there is not enough detail to determine whether the population in the studies matches that which is detailed within recommendations 1.1.50, 1.1.51 and 1.1.52.

Additional evidence indicates that antiviral therapy in pregnant women using tenofovir disoproxil or telbivudine reduces the risk of vertical transmission of HBV from mother to child when compared to no therapy given. Neither antiviral has market authorisation for use in pregnant women within the UK. However, using tenofovir disoproxil is recommended for 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 and the new evidence is unlikely to impact on current recommendations. Evidence on the use of telbivudine in pregnant women came from one small systematic review and it would be pertinent to await further evidence before including guidance on the use of telbivudine for pregnant women with hepatitis B.

New evidence is unlikely to change guideline recommendations.

Monitoring

Monitoring in people who do not meet criteria for antiviral treatment

Q – 11 How frequently should monitoring tests be done to ascertain virological, serological, biochemical response and resolution of fibrosis (HBeAg and antibody, HBsAg and antibody, ALT and transient elastography) and resistance (HBV DNA increase or virological breakthrough) in people with chronic hepatitis B?

Recommendations derived from this review question

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

1.6.9 Review injection technique and adverse effects weekly during the first month of treatment in people taking peginterferon alfa-2a [10].

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[10].

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[10].

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

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[10].

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[10].

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 [10].

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

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[10].

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[10].

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 'Children, young people and adults with compensated liver disease taking entecavir or lamivudine'[10].

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 'Children, young people and adults with compensated liver disease taking tenofovir disoproxil'[10].

Footnotes

Appendix A: summary of evidence from 4-year surveillance of Hepatitis B (chronic): diagnosis and management (2013) NICE guideline CG165

[10] At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Surveillance testing for hepatocellular carcinoma in adults with chronic hepatitis B

Q – 12 When and how frequently should surveillance testing be offered to detect early hepatocellular carcinoma in people with chronic hepatitis B?

Recommendations derived from this review question

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.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE's research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision will be taken on whether to retain the research recommendations or stand them down.

We applied the following approach to each of the following scenarios:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 Stopping antiviral treatment in HBeAg-negative disease

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.

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

It was proposed to remove the research recommendation from the NICE version of the guideline and the NICE research recommendations database because there is no evidence of research activity in this area. We considered the views of stakeholders after consultation. Therefore it was decided to retain this research recommendation based on the feedback on its importance.

RR – 02 ALT values for children and young people

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.

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

It was proposed to remove the research recommendation from the NICE version of the guideline and the NICE research recommendations database because there is no evidence of research activity in this area. We considered the views of stakeholders after consultation. Therefore it was decided to retain this research recommendation based on the feedback on its importance.

RR – 03 Long-term safety of tenofovir disoproxil in chronic hepatitis B

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.

- A longitudinal cohort study (n=585) assessed the efficacy, safety, and resistance of tenofovir disoproxil fumarate for up to 7 years (336 weeks) in HBeAg-positive and HBeAg-negative chronic hepatitis B patients. Long term treatment was associated with sustained virologic and serologic responses without resistance. The study reported no significant change in bone mineral density was observed from year 4 to year 7. Although this study is relevant to aspects of the research recommendation it does not fully report associated outcomes such as bone toxicity, risk of hypophosphataemia and cost effectiveness of routine monitoring. Due to these factors there is not enough evidence to suggest an update to the guideline is required at this stage.

Surveillance decision

This research recommendation will be retained because there is evidence of research activity in this area.

Appendix A: summary of evidence from 4-year surveillance of Hepatitis B (chronic): diagnosis and management (2013) NICE guideline CG165

RR – 04 Prophylactic treatment in people receiving immunosuppressive therapy

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.

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

It was proposed to remove the research recommendation from the NICE version of the guideline and the NICE research recommendations database because there is no evidence of research activity in this area. We considered the views of stakeholders after consultation. Therefore it was decided to retain this research recommendation based on the feedback on its importance.

Editorial and factual corrections identified during surveillance

During surveillance editorial or factual corrections were identified.

We will update the following footnote relating to drug licensing:

- Topic experts highlighted that Footnote 10 states that peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication.
    - Entecavir is now licensed for treating chronic HBV infection in nucleoside naive paediatric patients from 2 to < 18 years of age with compensated liver disease who have evidence of active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis.

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