GUIDELINES

Diagnosis and management of chronic hepatitis B in children, young people, and adults: summary of NICE guidance

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Chronic hepatitis B describes a spectrum of disease resulting from chronic hepatitis B virus (HBV) infection. About a third of the world’s population has serological evidence of past or present HBV infection, and 350-400 million people have chronic HBV infection. In the UK about 326,000 people are thought to have chronic hepatitis B. In some people, chronic hepatitis B may cause liver fibrosis, cirrhosis, and hepatocellular carcinoma; in others it is inactive and does not lead to important health problems. Antiviral therapy suppresses HBV replication and decreases the risk of progressive liver disease. This article summarises the most recent recommendations from the National Institute for Health and Care Excellence (NICE) on the diagnosis and management of chronic hepatitis B in children, young people, and adults.

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group’s experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

Assessment and referral in primary care

Children, young people, and adults who are seropositive for HBV surface antigen (HBsAg)

- Refer to a paediatric or adult hepatologist, gastroenterologist, or infectious disease specialist with an interest in hepatology.
- Arrange the following tests and include test results with the referral:
  - Hepatitis B e antigen (HBeAg, an indirect marker of high levels of viraemia and infectivity) or antibody status (anti-HBe, an indirect marker of lower levels of viraemia and infectivity)
  - HBV DNA level (quantitative direct measure of level of viraemia and infectivity)
  - IgM antibody to hepatitis B core antigen (IgM anti-HBc, evidence of recent infection with HBV)
  - Hepatitis C virus antibody (anti-HCV)
  - Hepatitis delta virus antibody (anti-HDV)
  - HIV antibody (anti-HIV)
  - Hepatitis A virus antibody (anti-HAV)
  - Alanine aminotransferase (ALT) or aspartate aminotransferase, y-glutamyltransferase, serum albumin, total bilirubin, total globulins, full blood count, and prothrombin time
  - Tests for hepatocellular carcinoma, including hepatic ultrasound and a fetoprotein testing.

Pregnant women who test positive for HBsAg at antenatal screening

- Refer pregnant women as above for assessment within six weeks of receiving the screening test result in order to allow treatment in the third trimester.

Assessment of liver disease in secondary specialist care

Throughout the following sections, “abnormal ALT” is defined as ≥30 IU/mL alanine aminotransferase for males and ≥19 IU/mL for females measured by two consecutive tests conducted three months apart.

Adults with chronic hepatitis B

- Offer transient elastography as the initial test to assess severity of liver disease and need for treatment:
  - For a transient elastography score ≥11 kPa, offer antiviral treatment (as below) without liver biopsy (as such patients are very likely to have cirrhosis and confirmation by liver biopsy is not needed).
  - For a transient elastography score between 6 and 10 kPa, consider liver biopsy to confirm the level of fibrosis and offer antiviral treatment (as below).

HBV is not cytopathic; it is the patient’s immune response to infected hepatocytes that results in progressive liver injury. The four phases of chronic hepatitis B result from variation in this immune response to viral antigens:

- Immune tolerance phase – HBeAg positive with high levels of viraemia (HBV DNA) with normal ALT levels, and minimal liver necro-inflammation.
- Immune clearance phase – Falling levels of HBe antigen and viraemia with elevated fluctuating ALT levels resulting from a developing antiviral response. There is a risk of progressive liver fibrosis.
- Immune control phase – HBeAg negative with very low or undetectable viraemia, normal ALT levels, and minimal necro-inflammation or fibrosis progression.
- Immune escape phase – HBeAg negative, positive for anti-HBe antibodies, increasing viraemia, elevated ALT levels, and necro-inflammation with progressive fibrosis.


Natural course of chronic hepatitis B virus (HBV) infection
Familial breast cancer: recognition, assessment and initial long term follow-up

- For a transient elastography score <6 kPa, offer liver biopsy and antiviral treatment (as below) if younger than 30 years with HBV DNA level >2000 IU/mL and abnormal ALT (adults with such a score are unlikely to have significant fibrosis). If ALT is normal and HBV DNA <2000 IU/mL, do not offer liver biopsy or antiviral treatment.

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

  Refer to the NICE guideline\(^5\) for recommendations regarding monitoring of liver disease or fibrosis of people in the immune tolerant phase of chronic hepatitis B (positive for HBeAg with high levels of HBV replication with normal ALT levels and minimal liver necro-inflammation) and in the immune control phase (negative for HBeAg with very low or undetectable levels of HBV DNA, normal ALT, and minimal fibrosis progression) (see figure for natural course of chronic HBV infection).

Patient information

Offer a personalised care plan outlining proposed treatment and long term management—for example, a copy of the hospital consultation summary.

Treatment criteria for adults

- Offer antiviral treatment to adults after consistent results from two consecutive tests conducted three months apart, as follows:
  - Patients aged ≥30 years who have HBV DNA levels >2000 IU/mL and abnormal ALT
  - Patients aged ≥30 years who have HBV DNA levels >2000 IU/mL and abnormal ALT if there is evidence of necro-inflammation or fibrosis on liver biopsy or a transient elastography score >6 kPa
  - Patients with HBV DNA levels >20 000 IU/mL and abnormal ALT regardless of age or the extent of liver disease
  - Patients with cirrhosis if any detectable HBV DNA is present, regardless of HBeAg status, HBV DNA levels, and ALT levels.

Treatment sequence

Refer to the NICE guideline\(^5\) for recommendations regarding monitoring to determine treatment response and adherence for each antiviral therapy in each population.

All adults (except those who are pregnant or breastfeeding or who are receiving immunosuppressive therapy)

- Offer a 48 week course of peginterferon alfa-2a as first line treatment.

Adults with HBeAg positive chronic hepatitis B and with compensated liver disease (in which liver fibrosis is present but liver function is preserved and stable)

- Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if the HBV DNA level has decreased by less than 100-fold and HBsAg has not decreased.
- Offer tenofovir or entecavir as second line treatment to people with detectable HBV DNA; offer a third line treatment option as described in the NICE guideline.\(^5\)
- Consider stopping nucleoside or nucleotide analogue treatment 12 months after achieving undetectable HBV DNA and HBsAg seroconversion in people without cirrhosis; do not stop treatment in people with cirrhosis.

Adults with HBeAg negative chronic hepatitis B and compensated liver disease

- Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if the HBV DNA level has decreased by less than 100-fold and HBsAg has not decreased.
- Offer tenofovir or entecavir as second line treatment to people with detectable HBV DNA; offer a third line treatment option as described in the NICE guideline.\(^5\)
- Consider stopping nucleoside or nucleotide analogue treatment 12 months after achieving undetectable HBV DNA and HBsAg seroconversion in people without cirrhosis; do not stop treatment in people with cirrhosis.

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

- Offer antiviral treatment if there is evidence of significant fibrosis or abnormal ALT on two consecutive tests conducted three months apart. See the NICE guideline for a full definition of significant fibrosis.\(^5\)
- Consider a 48 week course of peginterferon alfa-2a as first line treatment (see the NICE guideline for UK marketing authorisation for this drug).

Women who are pregnant or breast feeding

- Offer tenofovir to women with HBV DNA >10^7 IU/mL in the third trimester to reduce the risk of transmission of HBV to the baby (see the NICE guideline for UK marketing authorisation for this drug).

People starting immunosuppressive therapy

- Offer tests for anti-HBs antibodies, HBV DNA, HBeAg, and ALT in people who are seropositive for HBsAg or anti-HBc antibodies. Offer prophylaxis with entecavir or tenofovir if HBV DNA is >2000 IU/mL and consider the nucleoside analogue lamivudine otherwise. Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of six months after HBeAg seroconversion and HBV DNA is undetectable. Then monitor and manage according to the NICE guideline.\(^5\)
- In people who are HBsAg negative and anti-HBc positive and who are starting rituximab or other B cell depleting therapies, offer lamivudine as prevention against reactivation. Otherwise monitor and consider antiviral treatment as described in the NICE guideline.\(^5\)

Surveillance testing for hepatocellular carcinoma

- Perform six monthly surveillance for hepatocellular carcinoma by hepatic ultrasound and α fetoprotein testing in people with significant fibrosis or cirrhosis.
(see the NICE guideline for a definition of significant fibrosis). • In people without significant fibrosis or cirrhosis consider six monthly surveillance for hepatocellular carcinoma if the person is >40 years old, has a family history of hepatocellular carcinoma, or has HBV DNA ≥20000 IU/mL.

Adults with decompensated liver disease • Refer adults who develop decompensated liver disease immediately to a hepatologist or to a gastroenterologist with an interest in hepatology.

Adults co-infected with chronic hepatitis B and hepatitis C • Offer peginterferon alfa and ribavirin.

Adults co-infected with chronic hepatitis B and hepatitis delta • For adults co-infected with chronic hepatitis B and hepatitis delta and evidence of significant fibrosis, offer a 48 week course of peginterferon alfa-2a.

• Consider stopping treatment if HDV RNA is detectable after 6-12 months of treatment. Otherwise continue treatment and re-evaluate treatment response annually.

• Stop treatment after HBsAg seroconversion.

Overcoming barriers

Between 250 000 and 500 000 people in the UK are thought to have chronic hepatitis B. However, most cases are undiagnosed. Therefore, it is essential that this guideline is read in association with the NICE public health recommendations on improving case identification of HBV and HCV.

We recommend that essential serological tests are performed in primary care and that the results accompany the patient to the specialist to ensure more timely and efficient care.

Although costly, antiviral therapy can prevent downstream liver disease, reduce mortality, and improve quality of life. Based on best available evidence, the recommended sequence of therapies is the most effective and cost effective over the patient’s lifetime.

We recommend that the need for treatment is first assessed with transient elastography, minimising the need for invasive liver biopsy in some cases. Access to transient elastography is currently limited; this recommendation may require additional investment.

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2 Hepatitis B Foundation UK. Rising curve: chronic hepatitis B infection in the UK. 2008: www.hepb.org.uk/information/resources/rising_curve_chronic_hepatitis_b_infection_in_the_uk.

A PATIENT’S JOURNEY

Post-traumatic stress disorder after intensive care

Sarah Wake,1 Deborah Kitchiner2

This patient recounts her experiences of post-traumatic stress disorder after she received supportive treatment in intensive care.

Endless days and nights filled with strange broken sleep. A sea of fragmented menacing faces and shadows swimming through erratic beeps and bells. A large cackling face floating over me, constantly morphing and changing shape. The staring old lady in the bed opposite, her sallow skin disintegrating, eyeballs disappearing to reveal deep dark holes from which cockroaches crawled. Her weary face melting like wax into a big grey smudge. Deafening, haunting laughter filling every space. Blood seeping through holes and cracks in my skin, forming a puddle of red around me. Small insects scuttling up my arms and legs. My chest locked to the bed with wires and straps, as a plastic mask repeatedly smothered me. A strangling sensation around my neck. A warm metallic taste. An invisible force pinning my body down as a dark curtain was drawn closed.

These are my memories of intensive care. They formed the fabric of reality that I would take forward and recall vividly in my dreams for many months afterwards. Such fragmented delusional memories made it extremely difficult to understand and make sense of what really happened to me. This prevented my psychological recovery and led to the development of post-traumatic stress disorder (PTSD).

A surreal experience

In July 2011 I was coming towards the end of my foundation training, fit and excited about an upcoming month off and a trip to trek Mount Kilimanjaro. My day started as any other, struggling through a ward round, but ended as a patient intubated in intensive care. I had had an asthma attack, which was treated aggressively with salbutamol. Unfortunately my body reacted to the large dosage and I was pushed into severe metabolic acidosis, with
exhaustion, cardiac arrhythmia, and several biochemical imbalances as a result. I required supportive treatment in intensive care for many days.

While on the intensive care unit a combination of my illness, unnatural environment, sedatives, and opioids caused me to experience visual and tactile hallucinations and to feel extreme anxiety and confusion. I was repeatedly prescribed sedatives when I had episodes of chest pain, altered limb sensation, panic, and breathlessness. I now understand that a lot of these symptoms were caused by extremely high lactate levels, yet at the time I was offered no explanation and made to feel an anxious nuisance who could be silenced with a benzodiazepine. Ironically this would only increase my future delirium and confusion. My stay in the unit was prolonged while awaiting the availability of a lower dependency bed. As a result I became increasingly aware of my dynamic environment and formed vivid memories of surrounding sights, smells, and sounds.

Not only war veterans

PTSD has traditionally been associated with traumatic stressors such as combat, violent assault, and survival of natural disasters. Recently there has been increased awareness of symptoms occurring after critical illness and injury. Following a stay in intensive care, 1 in 10 patients develop symptoms of PTSD. It is one of the most common and most distressing, yet least talked about, problems associated with intensive care medicine. I had no warning about this association on my discharge. As a doctor I felt I was expected to be strong so initially hid my feelings of vulnerability and anxiety. I avoided speaking about what had happened. I didn’t want to get upset, upset anyone else, or return to the uncomfortable memories.

Return to darkness

Unbeknown to me at the time, the symptoms of PTSD can commonly take weeks to months to manifest. By this time I had started a rotation in a tertiary neonatal intensive care unit, with constant reminders of the intensive care environment. Gradually the sights, noises, and smells overwhelmed me. Flashbacks became increasingly intrusive. At night I dreaded going to sleep, as I would have vivid dreams where I was being intubated while fully conscious but unable to communicate. I experienced repeated sensations of suffocation and would awake coughing, breathless, and drenched in sweat. Usually a placid person, I began to feel very anxious, irritable, and easily startled. I couldn’t concentrate for any length of time and found myself “blanking off” frequently. After finishing a particularly busy shift, my chest became tight, my heart raced, and I became breathless. Feeling completely helpless and almost hysterical I knew I could not return to the hospital.

One of the key symptoms of PTSD is avoidance of any reminders of the stressor, and I took this to the extreme. I would make detours while travelling to avoid the sight of a hospital. I could not watch hospital documentaries or

**A CLINICIAN’S PERSPECTIVE**

It has long been recognised that people can develop psychological symptoms after their involvement in a major traumatic event. ICD-10 (international classification of diseases, 10th revision) classifies the trauma as an event “of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone.” This distressing reaction is more clearly defined in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, criteria of a response of fear, honor, or helplessness. In this case, Sarah experienced an asthma attack that led to intubation and treatment in intensive care. She described thinking she was going to die and feeling extremely helpless. PTSD symptoms include three subtypes; re-experiencing phenomena such as intrusive thoughts or recurrent dreams; avoidance and numbing; and increased arousal—for example, irritability or hypervigilance.

I treated Sarah for several months as an outpatient for PTSD. I used a trauma focused psychological therapy, eye movement desensitisation and reprocessing (EMDR) to process her traumatic memories, and graded exposure to help Sarah back to hospital environments and eventually back to work.

EMDR is one of two NICE recommended psychotherapies for PTSD. EMDR therapy shows that the mind can heal itself from psychological trauma much as the body recovers from physical trauma. EMDR is centered on the theory that bilateral stimulation allows traumatic memories to be processed. Bilateral stimulation is primarily eye movements but can be other types of stimulation such as hand taps or sounds. During EMDR the patient holds the worst image of the trauma in mind with the associated negative sensations and cognitions. The client then tracks the therapist’s hand as it moves back and forth across the client’s field of vision. Internal associations then arise and the client begins to process the memory and disturbing feelings. In successful EMDR therapy, the meaning of painful events is transformed on an emotional level.

During therapy Sarah’s memories were very jumbled up and she was often unsure as to what was real. Sedatives, such as benzodiazepines, can create disorientation and confusion, which can be extremely frightening for patients. Sarah regularly spoke of not understanding what was happening to her while on intensive care. She frequently described how nobody had explained things to her and she constantly felt confused and frightened. She was unable to communicate this at the time owing to sedation or intubation. If medical or nursing staff had explained what they were doing and what was happening every time they were with Sarah, even if she was unconscious, then this could have positively affected her experience.

PTSD after admission to intensive care is common and it is important that before they leave hospital patients are given information describing symptoms they may experience and where and when to seek help. Early intervention for PTSD can lead to better treatment outcomes.

Finally, support and understanding from medical colleagues to their peers is vital when someone experiences PTSD as Sarah did. Medical staff can feel that they should be immune to this kind of mental health problem. These sorts of attitudes can lead to feelings of shame and embarrassment, which can obstruct recovery.

Deborah Kitchiner, cognitive behaviour therapist
WHAT I HAVE LEARNT FROM THIS EXPERIENCE

- Mental health problems can affect anyone, regardless of status and circumstance. Unfortunately they remain poorly understood by many health professionals.
- The medical profession is poor at accepting and understanding colleagues with mental health problems, which I found highly frustrating. PTSD is a normal reaction, in normal people, to terrifying experiences. Despite this I often felt I was being weak and ridiculous owing to the reaction of those around me.
- The psychological aftercare of patients is currently neglected in the United Kingdom, with less than a third of hospitals offering support on discharge. The invisible psychological barriers patients need to overcome to return to their previous functioning can be more disabling and harmful than the initial period of physical illness.
- General practitioners in particular need to be educated about PTSD, as it is to them that affected people are most likely to present.
- The current treatment available on the National Health Service for patients with PTSD is poor, with few specialist centres and substantial waiting lists in excess of months. I was lucky to have financial help for excellent private treatment, yet for many this is not an option.
- Becoming an inpatient is a belittling experience. It is scary, lonely, and you feel helpless.
- Even if a patient has medical knowledge, it should not be assumed they understand the process occurring to them. I was often left without an explanation for the procedures and treatments I received and felt nursing staff thought I would rather be left alone. Frequent reassurance, explanation, and interaction with patients are vital in reducing the anxiety and fear associated with intensive care.
- Some of the associations increasing the risk of PTSD after a stay on the intensive care unit are modifiable. Medical professionals should be aware of the psychological side effects of certain drugs (in particular benzodiazepines) and avoid their use if possible.

Finding answers

People with PTSD usually recognise all too painfully that there is something drastically wrong, but are often unable to put a name to their feelings or symptoms. Worryingly a recent survey by Combat Stress (a charity working with veterans of the British armed forces helping to effectively put a name to their feelings or symptoms. Worryingly a recent survey by Combat Stress (a charity working with veterans of the British armed forces helping to effectively treat and support their psychological wounds, www.combatstress.org.uk) showed that fewer than half of general practitioners knew the official guidelines for diagnosing PTSD as set out by the then National Institute for Health and Clinical Excellence.

I visited my doctor several times, yet failed to receive a diagnosis. I was told I was being overly anxious and needed to relax. Each time I was met with a blank face, I felt increasingly isolated and lost.

In desperation I researched my symptoms and came across articles discussing the association between intensive care units and PTSD. With overwhelming relief I read similar patients’ experiences. I started a lengthy course of private psychotherapy involving exposure and eye movement desensitisation and reprocessing. I was initially cynical about this method, but it played a large part in my recovery. Gradually the distressing memories became less vivid, losing their intensity to become more organised ordinary memories. The thought of returning to a hospital environment became less uncomfortable. Using graded exposure I steadily progressed from nervously sitting in the hospital coffee shop to comfortably sitting in the intensive care to which I had been admitted.

Moving forward

Initially I wanted to resign from a career in medicine as I felt I would never be able to continue in my previous role, and had lost a lot of trust in the profession. However after four months of treatment I started to gradually return to work and successfully resumed full time work eight months after I had fallen ill. This was a massive step for me. Unfortunately I have discovered that certain events can still trigger flashbacks and lead to a depression that totally immobilises me. I am unable to work around ventilation equipment for long periods. As a result I cannot complete my paediatric training, although I am determined to continue my medical career in another specialty. I know this difficult experience will increase my understanding and empathy as a practising medical professional. I hope this article will bring awareness of the prevalence of anxiety, depression, and PTSD in patients after critical illness.

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STATISTICAL QUESTION

Open label crossover trials

Statements a, b, and d are true, whereas c is false.

CASE REPORT Hoarseness in a 79 year old woman

1 Hoarseness (dysphonia) can be caused by infections such as viral laryngitis, benign laryngeal lesions, laryngeal cancer, vocal cord paralysis, gastro-oesophageal reflux disease, neurological disease, hypothyroidism, and functional voice disorders.

2 The formation of an aneurysm (or pseudoaneurysm) of the aortic arch caused injury to the left recurrent laryngeal nerve, leading to vocal cord paralysis. This nerve passes around the aortic arch before ascending in the tracheo-oesophageal groove to supply the intrinsic muscles of the larynx.

3 Aortic aneurysm may be managed conservatively or with endovascular, open, or hybrid repair. The symptoms of vocal cord palsy may improve with time owing to compensation from the contralateral vocal cord; this process can be aided by speech therapy. Injections or surgical techniques are used to medialise the affected vocal cord when compensation is not sufficient.