National Institute for Health and Care Excellence

4-year surveillance (2017) – Hepatitis B (chronic): diagnosis and management (2013) NICE guideline CG165

Appendix B: stakeholder consultation comments table

Consultation dates: 19 July 2017 to 2 August 2017

Do you agree with the proposal not to update the guideline?

Stakeholder	Overall response	Comments	NICE response
British Infection Association	Yes	No comment	Thank you.
British Association for the Study of the Liver (BASL) & British Viral Hepatitis Group (BVHG)	Yes	No comment	Thank you.
UK Clinical Pharmacy Association	No	Update to nomenclature for natural history for chronic states. Review to recommend of treatment to patients over 30 with **normal** ALT and high HBV DNA regardless of liver histology.	Thank you for your comment. The recommendation published by the EASL states: Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions is based on the 'opinions of respected authorities, descriptive epidemiology'. No evidence in this area was identified through the surveillance review to support a change to the guideline in this area.
Consultation Group on Hepatitis Topics, representing the British HIV Association (BHIVA) and the British Association for Sexual Health and HIV (BASHH)	No	There have been a number of important innovations/changes since this guidance that will impact patient care in England and Wales: a) Publication of the WHO targets for reduction in new incidence and mortality for HBV and HCV b) Update of EASL, AASLD Hep B guidelines and publication of the WHO guidance on the diagnosis, assessment and management of HBV	Thank you for your comments. The WHO targets are global in their nature, the recommendations published in 2015 are generally in line with those within this guideline. The updates to the EASL (European) and AASLD (United States) hepatitis B guidelines are set within practices where funding streams differ from that within the UK. In addition, no relevant published

		c) More data on the efficacy (or lack of) and HBsAg and HBV DNA based stopping rules for the use of Peg-IFN-alpha d) More data on finite therapy with nucleos(t)ides e) Approval of Tenofovir-Alafenaimde (TAF) for the treatment of HBV f) Data on the use of oral antivirals to prevent mother-to-child transmission of HBV g) Data on the risk of HBV re-activation post successful HCV treatment in co-infected patients h) Roll-out of TDF/FTC for HIV post-exposure prophylaxis, and the need for HBV testing in 'at risk' groups AND the need to avoid TDF 'mono-therapy' for the treatment of chronic HBV in patients also requiring HIV pre-exposure prophylaxis We urge the committee to reconsider this decision. The current guidance, unfortunately, provides for sub-standard care in this highly vulnerable group of patients.	evidence was found from this surveillance review indicating that a change in recommendations is required. The recommendation published by the EASL states: Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions is based on the 'opinions of respected authorities, descriptive epidemiology'. No evidence in this area was identified through the surveillance review to support a change to the guideline in this area. Unfortunately, although there is published evidence of its use on participants within clinical trials, tenofovir alafenamide does not currently have approval for the treatment of HBV in the UK. We will consider this again at the next surveillance of the guideline. Unfortunately there is no new published evidence regarding the risk of HBV re-activation post successful HCV treatment in co-infected patients that would impact the current recommendations. We will consider this again at the next surveillance of the guideline. HBV testing and people co-infected with HIV are not within the scope of this guideline so it is not possible to make recommendations in these areas. Please see NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection for recommendations regarding HBV testing. All relevant evidence since the publication of the guideline was considered as part of the surveillance review and none was found which would impact on the current guidelines.
Roche Diagnostics Ltd	No answer	No comment	Thank you.
Hepatitis b positive trust	No	We have a booming undiagnosed migrant population of chronic hbv patients, now is not the time to decide to carry on our massive lacking of testing for HBV.	Thank you for comment. HBV testing is not within the scope of this guideline so it not possible to make recommendations in this area. Please see NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection for recommendations regarding HBV testing of migrant populations.
Public Health England	Yes	There is insufficient new information to update current guidance	Thank you for your comment.

Do you agree with the proposal to remove the research recommendation?

RR – 01 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.

Stakeholder	Overall response	Comments	NICE response
British Infection Association	Yes	No comments received	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
British Association for the Study of the Liver (BASL) & British Viral Hepatitis Group (BVHG)	Yes	No comment	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
UK Clinical Pharmacy Association	Yes	No comment	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
Consultation Group on Hepatitis Topics, representing the British HIV Association (BHIVA) and the British Association for Sexual Health and HIV (BASHH)	No Answer	No comment	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
Roche Diagnostics Ltd	No	We believe that use of the HBsAg quantitative assays (either alone or in combination with HBV DNA levels) are valuable tools in determining treatment duration in hepatitis B e antigen (HBeAg) negative patients and that this research recommendation should remain. We refer the Committee to the recent publication Cornberg M, Wai-Sun Wong V, Locarnini S, et al. Journal of Hepatology 2017; 66: 398–411 and the references within in to recent data on HBsAg levels in HBeAg negative patients receiving treatment (e.g. Marcellin P et al. Hepatology International 2013; 7(1): 88–97; Goulis I et al. Liver International 2015; 35(5):1540-48; Seto WK. Gut 2014; 64:667-	Thank you for your comment. We decided to retain this research recommendation based on the feedback on its importance.

		672). However, there is a need to determine the clinical and cost-effectiveness in a UK population and as such this research recommendation is still valid and should remain.	
Hepatitis b positive trust	No	It is remarkable that we even need to evaluate this. HBV causes very expensive treatments once cirrhosis and cancer emerges. We have booming levels of both, we are planning to watch cost effective mass screening remain undiscovered exactly when we need to rapidly increase such testing.	Thank you for your comment. We decided to retain this research recommendation based on the feedback on its importance.
Public Health England	No	Serum hepatitis B surface antigen (HBsAg) is a reliable marker of overt hepatitis B virus (H BV)infection **(1)**, Several studies,(Peg-Interferon based) have shown kinetics of HBsAg to predict a response to antiviral therapy, the predictive value of HBsAg being important for both treatment and interpretation of the phases of HBV infection in untreated patients (2). **(1) Clinical Implications of HBsAg Quantification in Patients with Chronic Hepatitis B** Viganò, Lampertico Saudi J Gastroenterol. 2012 Mar-Apr; 18(2): 81–86 (2) **Kinetics and Prediction of HBsAg Loss during Long-Term Therapy with Nucleos(t)ide Analogues of Different Potency in Patients with Chronic Hepatitis B.** Li et al. Plos One June 2014 https://doi.org/10.1371/journal.pone.0098476 HBsAg is important as a measure of stopping rates especially in children undergoing peg-interferon therapy which help to guide the management of the patient. In theory the use of quantification for HBsAg gives an indirect measure for translational capacity of covalently closed circular deoxyribonucleic acid (cccDNA). This surely needs to be explored in more detail. At present integrated or autosomal cccDNA represents the site and mode of viral persistence even once ribonucleic acid (RNA) transcriptase has been inhibited. Such residual genomic sequences may become translational reactive and long-term therapy is required to achieve eventual clearance of HBV DNA from the liver. **(3) Persistence of hepatitis B virus covalently closed circular DNA in hepatocytes: molecular mechanisms and clinical significance** Yang and Kao Emerg Microbes Infect. 2014 Sep; 3(9	Thank you for your comment. We decided to retain this research recommendation based on the feedback on its importance.

Do you agree with the proposal to remove the research recommendation?

RR – 02 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

Stakeholder	Overall response	Comments	NICE response
British Infection Association	Yes	No comments received	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
British Association for the Study of the Liver (BASL) & British Viral Hepatitis Group (BVHG)	Yes	No comment	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
UK Clinical Pharmacy Association	Yes	No comment	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
Consultation Group on Hepatitis Topics, representing the British HIV Association (BHIVA) and the British Association for Sexual Health and HIV (BASHH)	No Answer	No comment	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
Roche Diagnostics Ltd	No Answer	No comment	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
Hepatitis b positive trust	No	There is a clear case for understanding as deeply as we can the impact of raised alt scores in causing end stage liver disease and being aware through due diligence of when alts scores indicate treatment. Further with HBV children showing 1% end stage liver disease at 16 such studies are needed. Further children are testing 1 in 250 infected with HBV in the NHS venues where we test them, so	Thank you for your comment. We decided to retain this research recommendation based on the feedback on its importance.

		the need is great indeed for us to know the relationship of alts scores in their disease development.	
Public Health England	No	Transaminitis, identified by measuring alanine aminotransferase (ALT) values is a valid determinant of the liver inflammation. Normal values for non-adults may be more accurate for inferring ongoing liver disease. Transaminitis is however not a marker for viral replication in most situations although a return of ALT to normal may be of use in some situations. PHE would not recommend using serum ALT as a marker in isolation for virological activity when considering whether to continue or discontinue treatment. (4) Monitoring During and After Antiviral Therapy for Hepatitis B. Andersson and Chung Hepatology. 2009 May; 49(5 Suppl): S166–S173	Thank you for your comment. Using serum ALT as a marker in isolation for virological activity when considering whether to continue or discontinue treatment is not currently recommended. However, we have decided to retain this research recommendation based on the feedback on its importance.

Do you agree with the proposal to remove the research recommendation?

RR – 04 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.

Stakeholder	Overall response	Comments	NICE response
British Infection Association	No	This is an ongoing question	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
British Association for the Study of the Liver (BASL) & British Viral Hepatitis Group (BVHG)	Yes	No comment	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
UK Clinical Pharmacy Association	Yes	No comment	Thank you. We decided to retain this research recommendation based on the feedback on its importance.

Consultation Group on Hepatitis Topics, representing the British HIV Association (BHIVA) and the British Association for Sexual Health and HIV (BASHH)	No Answer	No comment	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
Roche Diagnostics Ltd	No Answer	No comment	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
Hepatitis b positive trust	No	We have received reports of traumatic reactivation and deaths from HCV anti virals and from chemotherapy for leukaemia. Are we to await and risk patient deaths before we do research at a time when the CDC is black box warning on HCV anti virals a year before we do?	Thank you. We decided to retain this research recommendation based on the feedback on its importance.
Public Health England	No	This question is not answerable unless the originators define what they mean by mild immunosuppressive agents. For example the widespread use of drugs like rituximab have a profound benefit for people with musculoskeletal disease. The individual whose plasma contains anti-HBc is always susceptible to potentially adverse conditions depending on their exposure to immunosuppressive drugs. Even the immunosuppression associated with haemodialysis in the absence of any therapy is sufficient in some people to trigger reactivation of HBV. There is a broad lack of awareness of the risk involved and the need to consider whether a patient about to undergo even if mild immunosuppression, should be screened for anti-HBc. The use of suppressive intervention may be important and should be further investigated.	Thank you. We decided to retain this research recommendation based on the feedback on its importance.

Do you have any comments on areas excluded from the scope of the guideline?

Stakeholder	Overall response	Comments	NICE response
British Infection Association	No	No comments	Thank you.
British Association for the Study of the Liver (BASL) &	No	No comments	Thank you.

British Viral Hepatitis Group (BVHG)			
UK Clinical Pharmacy Association	No	No comments	Thank you.
Consultation Group on Hepatitis Topics, representing the British HIV Association (BHIVA) and the British Association for Sexual Health and HIV (BASHH)	No Answer	No comment	Thank you.
Roche Diagnostics Ltd	No Answer	No comment	Thank you.
Hepatitis b positive trust	Yes	Testing at our borders could diagnose the 2.2% of migrants with hbv and save many lives. Testing at GP registration or A n E could help to diagnose the estimated 300,000 undiagnosed highly infectious carriers and save much time, money and morbidity. We have good guidelines for clinical care that 75% of patients cannot access due to poor testing. Further we are missing the key point only 20% of patients need clinical care as they are healthy carriers, but 80% need social and emotional support and education which is lacking in many easy fix areas. Suicide, depression, lost jobs, lost loves, lost children and general ignorance are causing huge morbidity and yet we are not addressing what patients and public know and are being taught. Our children need catch up vaccs as well as birth doses, our hbv information needs to understand hbv is a child virus for most UK patients now, our care program needs diagnostic skills that find inform and empower patients rather than confusing and traumatising them.	Thank you for your comment. Unfortunately HBV testing and vaccination is not within the scope of this guideline so it is not possible to make recommendations in this area. Please see NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection for recommendations regarding HBV testing of migrant populations.
Public Health England	Yes	The guidelines should outline and ensure public health follow-up and best practice management of contacts of chronic cases of hepatitis B infection. To therefore include recommendations on the administration of post exposure hepatitis B vaccine and specific hepatitis B immunoglobulin (HBIG) to contacts of those persistently infected where appropriate. (5) Immunisations against Infectious Disease The Green Book Chapter 18	Thank you for your comment. The guideline cross refers to the NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. This clinical guideline should be used in conjunction with the public health guideline which provides guidance on vaccinations for close contacts.

Do you have any comments on equalities issues?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
British Infection Association	No	No comments	Thank you.
British Association for the Study of the Liver (BASL) & British Viral Hepatitis Group (BVHG)	No	No comments	Thank you.
UK Clinical Pharmacy Association	No	No comments	Thank you.
Consultation Group on Hepatitis Topics, representing the British HIV Association (BHIVA) and the British Association for Sexual Health and HIV (BASHH)	No Answer	No comment	Thank you.
Roche Diagnostics Ltd	No Answer	No comment	Thank you.
Hepatitis b positive trust	Yes	Our BME communities, vulnerable children and elderly adults are disproportionately getting infected, being undiagnosed and dying of HBV. We need to focus a awareness campaign and de stigmatised information at this group. To date the bulk of our HBV diagnosis are 3 month pregnant mothers and we still have no decent hbv education or helpline budget to help them with. Further the 35,000 children indicated to be HBV positive due to our delay in vaccinating need to be found. The gross inequalities and unmet needs of the UK HBV patient population simply cannot afford the type of neglect and lack of diagnosis for a longer period. Kicking this topic into the long grass for however long is decided will cost us all more infections, more end stage liver disease and an ongoing cohort of poorly served patients.	Thank you for your comment. The recommendations on screening of pregnant mothers for HBV are currently found within the PHE document: NHS Infectious Diseases in Pregnancy Screening Programme - Standards 2016 to 2017. All positive tests would be referred for treatment as per the appropriate pathway. Since autumn 2017 all new-borns are now offered Hepatitis B vaccinations. Please see Hexavalent combination vaccine: routine programme guidance (PHE 2017)

Public Health England	Yes	The area where inequality is most likely to occur is during patient assessment and referral in primary care in many cases due to language and communication issues. Like so many infections which exhibit ethnic traits, infected people in these groups may well be at a disadvantage either through language, poverty or healthcare attitudes. Breaking down these barriers and improving diagnostics for the identification of individuals and affected households are important and challenging.	Thank you for your comment. The guideline cross refers to the NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. Recommendation 2 deals with awareness raising for people at increased risk of hepatitis B stating that material should address the needs of non-English-speaking groups at increased risk e.g. providing translated information and should be culturally and age appropriate. This clinical guideline should be used in conjunction with the public health guideline.

Royal College of Paediatrics and Child Health

We have not received any responses for this consultation

The British Society for Antimicrobial Chemotherapy

Members of The British Society for Antimicrobial Chemotherapy (BSAC) have no comments for this **Quality standard topic engagement exercise – CG165 Hepatitis B (chronic).**

Royal College of Nursing

No comments to submit at this stage