NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Hepatitis B Infection Assessment and Management in Adults

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

Assessment and management of Adults with hepatitis B infection

NHS Greater Glasgow and Clyde

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Introduction

This guideline is based upon guidelines from the European Association for the Study of the Liver (EASL) 2017 (1), and American Association for the study of Liver Diseases (AASLD) 2018 (2).

Around 240 million people in the world are chronic hepatitis B (CHB) carriers. The prevalence is Scotland is estimated to be around 0.2%, with around 9000 persons thought to be CHB carriers in 2012 (3). Morbidity and mortality in CHB are linked to persistence of viral replication and evolution to cirrhosis and/or hepatocellular carcinoma (HCC).

Natural History of Hepatitis B Virus (HBV) infection

The spectrum of disease and natural history of chronic HBV infection are variable. Chronic HBV infection is a dynamic process, reflecting the interaction between HBV replication and the host immune response. Several stages of infection are described (figure 1). Patients may move between these stages and regular monitoring of HBeAg, HBV DNA and ALT and of liver fibrosis are essential so correct treatment decisions can be made appropriate to the phase of infection.

	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml°°	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

Figure 1. Stages of Hepatitis B infection (1)

Approximately 0.5% per annum of patients will spontaneously clear their HBsAg during the natural course of infection, with or without the development of anti-HBs(1).

Immunosuppression, even after loss of HBsAg may lead to viral reactivation. This is covered in a separate NHS GGC guideline – HBV Reactivation – available on the intranet.

New Patient Assessment

History to include:

- Assessment of probable route and duration of infection, country of birth
- Family History of CHB infection, liver cancer and cirrhosis
- Previous HBV Therapy
- Results of HBV tests / vaccinations of close and sexual contacts
- Advice on risk factors for transmission: condoms, vaccination of household and sexual contacts, not to share toothbrush or razors, cover cuts and clean up blood spills etc.
- Other medication / drugs / alcohol
- Future and current fertility and contraception plans

Examination

- Stigmata of Chronic Liver Disease
- Liver palpation

Investigations

- If not already done, the following tests should be arranged:

Blood Tests

Virology	HCV IgG / HAV IgG	**Haematology**	FBC
	HIV Test (with verbal consent)		Coagulation
	HBV-serology (sAg, cAb, eAg, eAb)		Ferritin
	HBV PCR		Iron Studies
	HDV PCR (routinely tested on all new HBV patients)		
Biochemistry	U&E + Glucose + TFT Bone Profile (phosphate)	**Immunology**	Autoantibodies: ANA, AMA, ASMA and LKM
	LFT including gamma GT		
	Alphafetoprotein (AFP)		
	Caeruloplasmin		
	Alpha-1-antitrypsin		
	Immunoglobulins		

Table 1. Baseline blood testing

HBV Genotypiung is not done routinely, but may be available after discussion with the West of Scotland Virology lab in GGC

Imaging

- Fibroscan
- Liver Ultrasound Scan

Liver Biopsy

- Liver biopsy is the gold standard for assessing the degree of inflammation and fibrosis. Biopsy is most useful in those who do not meet clear criteria for treatment and where there is uncertainty about the cause of liver disease. Biopsy should not be performed on patients with cirrhosis.

Contact Tracing and Vaccination

- Advise HBV testing and / or vaccination of household or sexual contacts if this has not already been done. Since 2012, all new HBV cases (chronic or acute) are automatically notified to the BBV Failsafe team at Sandyford who will support GPs and other health Professionals in arranging contact tracing and vaccination.

Treatment Aims

Loss of HBsAg is rarely achieved with current treatments and the primary aim of treatment is to prevent the development of liver cirrhosis and HCC by suppressing HBV viral replication. Additional goals of antiviral therapy are to prevent mother to child transmission, and hepatitis B reactivation.

Treatment outcomes associated with improved prognosis may be divided into biochemical, virological and serological responses.

- Biochemical – normalization of ALT
- Virological - with PegIFNα – HBV DNA < 2000 IU/ml 6 months after completion of therapy - With Nucleotide analogues - HBV DNA <10 IU/ml on treatment
- Serological – for HBeAg+ patients: loss of HBeAg +/- seroconversion to anti-HBe

In addition, there is evidence that sustained suppression of viral replication may lead to histological improvement in patients with established cirrhosis.

Indications for treatment

The indications for treatment for both HBeAg-positive and HBeAg-negative CHB and are based on HBV DNA levels, ALT levels and liver fibrosis (usually assessed by fibroscan)

EASL 2017 suggests an ALT Upper Limit of Normal (ULN) of 40 IU/ml (1).
AASLD 2018 uses an ULN for ALT of <19 IU/ml for women and <30 IU/ml for men (2).

EASL (2017) Treatment Recommendations:

Strong Recommendation

- HBV DNA >20,000 IU/ml and ALT >2xULN - regardless of the degree of fibrosis
- Patients with compensated or decompensated cirrhosis, with any detectable HBV DNA level and regardless of ALT
- Patients with HBV DNA >2,000 IU/ml, ALT >ULN and at least moderate fibrosis (liver stiffness >9 kPa on Fibroscan (4))

Weaker recommendation

- Patients with HBeAg-positive HBV, persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver fibrosis
- Patients with HBeAg +/- HBV and family history of HCC or cirrhosis can be treated even if typical treatment indications are not fulfilled

Indications for treatment should also take into account the patients' age, health status, risk of HBV transmission and extrahepatic manifestations.

Monitoring of patients currently not requiring treatment

Most patients with CHB do not require treatment. However close monitoring is essential so correct treatment decisions can be made appropriate to the phase of infection

	HBeAg positive	**HBeAg negative** **HBV DNA <2,000 IU/ml**	**HBeAg negative** **HBV DNA >2,000 IU/ml**
ALT	3-6 months	12 months	6 months
AFP	6 months	12 months	6 months
HBV DNA	6 months	12 months	6 months
Fibroscan	12 months	2-3 years	12 months

Table 2: Suggested monitoring schedule for patients not on treatment

Surveillance for Hepatocellular Carcinoma (HCC) must also be considered (see below).

Treatment Recommendations for Non-cirrhotic CHB

Two types of treatment are used for CHB; pegylated interferon alpha (PegIFNα) or nucleoside/nucleotide analogues (NAs). Both are NHS GGC formulary approved for the treatment of HBeAg-positive or HBeAg-negative CHB. Advantages and disadvantages of both types of treatment are listed in figure 2 (1).

The main advantage of treatment with a potent NA is its predictable long-term antiviral efficacy leading to undetectable HBV DNA levels in the vast majority of compliant patients as well as its favourable safety profile. The rationale for a PegIFNa based approach is to induce longterm immunological control with a finite duration treatment. The main disadvantages of PegIFNα treatment is the high variability of response and its unfavourable safety profile.

Choice of first line therapy is influenced by patient characteristics and informed patient choice. Factors to consider include; route of administration, side effects, likely treatment duration, familyplanning, ALT, HBV DNA, liver histology or Fibroscan result, genotype and family history.

A high level of adherence to NA therapy is critical for virological outcome and to prevent resistance.

Ensure the patient is HIV negative before starting NA therapy.

Table 2. Main concepts and features of current treatment strategies of chronic hepatitis B.

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss (stopping NA after some years might be considered in selected cases)[1]
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment adverse events (psychiatric, neurological, endocrinological)	Probably not (uncertainties regarding kidney function, bone diseases for some NA)
Contraindications	Many (*i.e.*, decompensated disease, co-morbidities etc.)	None (dose adjustment according to eGFR[2])
Strategy	Induction of a long-term immune control by finite treatment	Stopping hepatitis and disease progression by inhibiting viral replication
Level of viral suppression	Moderate (variable response pattern)	Universally high
Effect on HBeAg loss	Moderate, depending on baseline characteristics	Low in the first year, increases to moderate during long-term treatment
Effect on HBsAg levels	Variable, depending on baseline characteristics (overall higher as compared to NA)	Low: slowly increases with treatment time in HBeAg-positive patients[3]; usually very low in HBeAg-negative patients
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance development	No	Minimal to none[4]

PegIFNα, pegylated interferon alfa; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; NA, nucleoside/nucleotide analogues; eGFR, estimated glomerular filtration rate.

Figure 2. Advantages and disadvantages of PegIFNα and NAs in the treatment of CHB (1)

Pegylated Interferon Alpha 2a

PegIFNα is given as a weekly subcutaneous injection. Treatment is usually for 48 weeks but may be stopped early if a stopping rule is reached or due to intolerance. PegIFNα has many side-effects, including flu-like symptoms,fatigue, bone marrow suppression, depression, and exacerbation or unmasking of autoimmune illnesses. It is contra-indicated in pregnancy, patients with autoimmune disease, uncontrolled seizures, significant psychiatric disease and decompensated cirrhosis and should be used with caution in patients with compensated cirrhosis.

	HBeAg-positive patients	*HBeAg-negative patients*
HBV DNA <2000 IU/ml (%)	14	19
Anti-HBe seroconversion (%)	32	N/A
ALT normalisation (%)	41	59
HBsAg loss (%)	3	4

Table 3. Response rates at 6 months following after 48 weeks of PegIFNα (1).

Pre-treatment predictors of a favourable response to PegIFNα (1,2)

e-Ag Positive

- Genotype A or B > C or D
- ALT ≥2-5 x ULN
- HBV DNA < 10^8 IU/ml (log 8)

e-Ag Negative

- Age <30
- Genotype B or C > D
- ALT > ULN
- Female sex

On treatment predictors of response to PegIFNα

E-Antigen Positive patients

On treatment quantitative HBsAg levels (QsAg) can be used to identify HBeAg positive patients who are unlikely to respond. In NHS GGC, genotyping of HBV is not routinely performed, so interpretation of a week 12 QsAg result is difficult. A genotype may be requested from the Virology lab when PegIFNα treatment is being considered.

- **Week 12 -**
  - Patients with Genotype B or C who have a QsAg > 20,000 IU/ml are unlikely to respond to therapy and should stop
  - Patients with Genotype A or D with no decline in QsAg levels are unlikely to respond to therapy and should stop

- **Week 24 –**
  - All Genotypes, a QsAg level of >20,000 IU/ml indicatied patients are unlikely to respond to therapy and should stop

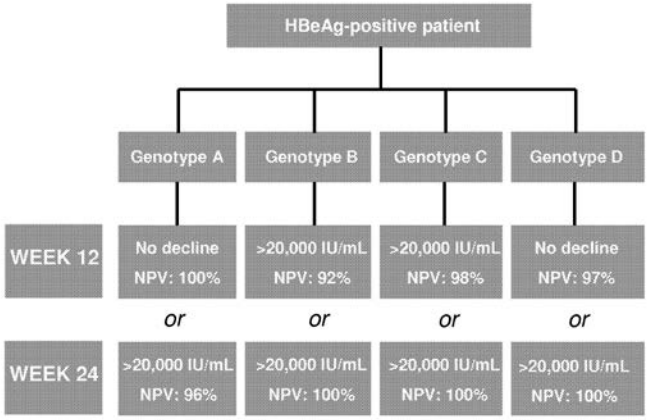

Figure 3. Stopping rules using QsAg in HBeAg-positive patients treated with PegIFNα (1)

E-Antigen Negative patients

Stopping rules for e-Ag negative patients on PegIFNα are less well established. At **week 12**, a combination of no HBsAg decline and <2 log10 IU/ml decline of HBV DNA predicts nonresponse in HBeAg-negative patients with genotype D and should be used as a stopping rule (1).

Nucleoside/Nucleotide analogue (NA) therapy

Tenofovir disoproxil fumarate (TDF) and Entecavir are potent anti-virals with high barriers to resistance. EASL recommend ETV over TDF for patients >60 yrs, those with pre-existing renal disease or osteoporosis. TDF is the drug of choice if required in pregnancy. ETV should be used with caution in previously Lamivudine treated patients in case of resistance.

TDF requires monitoring for renal side-effects. A newer version of tenofovir, tenofovir alafenamide, has no renal side-effects and is licensed for Hep B treatment. It is not approved by Scottish Medicines Consortium (SMC) for use in patients with CHB unless HIV co-infected.

Data from clinical trials on treatment response after 1 year with NAs in HBeAg-positive and negative patients are shown in table 6 (1). These trials were conducted in different patient populations and the response rates are not directly comparable. With prolonged therapy, response rates increase.

	TDF	**Entecavir**	**TAF**
Treatment responses at 1 year in HBeAg-positive patients			
Anti-HBe seroconversion (%)	21	21	10
HBV DNA <60 IU/ml (%)	76	67	64
ALT Normalisation (%)	68	68	72
HBsAg Loss (%)	3	2	1
Treatment responses at 1 year in HBeAg-negative patients			
HBV DNA < 60 IU/ml (%)	93	90	94
ALT Normalisation (%)	76	78	83
HBsAg Loss (%)	0	0	0
Resistance at 1 year (%)	0	<1	0
Resistance at 5 years (%)	0	1	N/A

Table 4. Treatment response and resistance rates with NAs in HBeAg-positive and negative patients, and resistance rates (1)

Less potent NAs including Lamivudine, Adefovir and Telbivudine are not recommended for treatment.

Shared care protocols for the management of chronic HBV are available in GGC to define the roles for GPs and hospital specialists in the management of CHB.

http://www.ggcprescribing.org.uk/shared-care-protocols/

A specialist should always recommend the initiation of Hep B treatment but prescribing is usually undertaken by GPs. Monitoring of treatment efficacy and for side-effects will be undertaken in the specialist clinic. Where treatment is required to start immediately then the initial supply will be dispensed from secondary care, with the GP providing ongoing prescribing if required, e.g. in late pregnancy.

Community pharmacies can order NAs for patients who have these drugs prescribed by their GPs. To avoid delays in this process, patients should be advised to present their repeat prescition several days in advance. A letter detailing how community pharmacies can order these drugs should be given to patients from hospital clinics to take to their pharmacists, **Appendix 1.**

Combination or Sequential PEG-IFN and NA therapy

At the present time, none of the published guidelines recommend treatment using combinations of PEG-IFN plus NAs, or using these drugs sequentially.

Monitoring of Patients on Treatment

- **Pegylated interferon:**

Time	Test
Every 3 months on treatment	FBC, UE, LFT, TFT, HBV DNA
+ At 3 months	HBsAg Quant
+ At 6 months	AFP, HBeAg, anti-HBe, HBsAg Quant
+ At End of treatment	AFP, HBeAg, anti-HBe
+ 6 and 12 months post treatment	AFP, HBV DNA, HBeAg, anti-HBe

Table 5. Monitoring on IFN treatment

See **Appendix 2**

- **Tenofovir / Entecavir:**

Time	Test
Every 3-6 months	LFT, AFP, HBV DNA. If on TDF: UE, urine Protein Creatinine Ratio (uPCR), Bone profile
HBeAg positive	HBeAg, anti-HBe every 12 months
Undetectable HBV DNA	Check HBsAg every 12 months and if clear HBsAg then check anti-HBs

Table 6. Monitoring on NA treatment

Treatment Discontinuation of NAs

- NA treatment should NOT be discontinued in patients with significant liver fibrosis
- For both **eAg-positive** and **eAg-negative** patients, treatment discontinuation can be considered in non-cirrhotic patients who achieve sAg loss.
- For e**Ag-positive** non-cirrhotic patients, NAs may be discontinued in those who achieve anti-HBe seroconversion and have undetectable HBV DNA. Treatment should continue for at least 12 months following e-seroconversion prior to stopping.
- For **eAg-negative** non-cirrhotic patients, NAs discontinuation after a prolonged period of HBV DNA undetectability has been suggested but the optimum duration of suppression is not known. Approximately 50% of patients remain in remission after NA cessation after at least 2 years of DNA suppression on treatment
- Close monitoring is required as a number of these patients will require retreatment as they will not sustain their virological, serological or biochemical response.
- No reliable predictor of post-NAs remission has been identified to date. Using quantification of sAg levels is not recommended in the current EASL or AASLD guidelines.

The Role of Quantitative Surface Antigen Assessment (QsAg)

QsAg measurement is available in GGC. The clinical utility of this test is still being defined. EASL suggests its use in the following situations:

- **Patients receiving PegIFNα -** QsAg levels during treatment to identify patients likely to respond, and allowing treatment to be stopped early when futile

- **HBeAg-negative patients with HBV DNA <2,000 IU/ml** – consider QsAg measurement to guide frequency of liver fibrosis assessments
    - If HBsAg levels <1,000 IU/ ml - liver fibrosis assessments every 3 years

    - If HBsAg levels >1,000 IU/ml - liver fibrosis assessment at least every 2 years

Screening for Hepatocellular Carcinoma (HCC)

The risk of developing HCC is higher in patients with cirrhosis, chronic hepatic necroinflammation, older age, male sex, African origin, alcohol abuse, co-infections with other hepatitis viruses or HIV, diabetes or metabolic syndrome, active smoking, positive family history and/or to HBV properties (high HBV DNA and/or HBsAg levels, HBV genotype C > B, specific mutations).

Several risk scores have been recently developed for HCC prediction in CHB patients but they have not been validated in all regions and patient groups. EASL, AASLD and NICE guidelines differ in their recommendations and there is no agreed standard.

The following is a suggested outline for use in GGC but clinics may differ from this.

Liver ultrasound with AFP measurement every 6 months in the following CHB patients:

- Patients with significant liver fibrosis or cirrhosis.
- Males over 40 years old
- Females over 50 years old
- Patients with a 1st degree relative with a history of HCC
- Sub Saharan Africans (any age) - HCC occurs at a younger age in this group

Treatment of Special Populations

1. Compensated cirrhosis

Should be managed by hepatologists. Treatment with NAs is likely to be indefinite.

2. Decompensated cirrhosis / Post liver transplant

Should be managed by hepatologists +/- in conjunction with Scottish Liver Transplant Unit (SLTU). These patients should be treated with a NA irrespective of HBV DNA levels. Do not use PegIFNα. Note: Entecavir was rejected by SMC for decompensated cirrhosis.

3. Hepatitis D co-infection

HBV-HDV co-infection is associated with faster liver disease progression. PegIFNα is the only effective drug against HDV (1). The optimal duration of therapy is not well defined and is at least 48 weeks. NAs do not impact on HDV replication but should be considered in those with ongoing HBV replication following IFN treatment.

4. Hepatitis C Virus (HCV) co-infection

HCV rather than HBV is often responsible for the chronic hepatitis seen in this group of patients. Patients should receive HCV as required. Treatment of hepatitis C with new direct acting antivirals has been associated with reactivation of hepatitis B. See GGC HBV Reactivation Guideline.

5. HIV co-infection

Co-infected patients should be managed by infectious disease physicians. Entecavir should never be used unless the patient is also taking antiretroviral medication. All patients should be TAF/TDF bases ART.

6. Acute HBV infection

Most adults with acute HBV will recover spontaneously. No clear benefit from NA therapy has been demonstrated though this should be considered in patients with fulminant hepatitis.

Pregnancy

A separate NHS GGC policy on the management of CHB in Pregnancy is available on the GGC intranet. Briefly, in all pregnant women with high HBV DNA levels (>200,000 IU/ml, log 5.3), treatment with tenofovir should start at week 24–28 of gestation and continue for up to 12 weeks after delivery.

Tenofovir is classified as a category B risk in pregnancy but has been used widely in HIV+ women of child bearing age with no discernible harm. Children born to CHB mothers should receive vaccination +/- Hepatitis B immunoglobulin as per national guidelines. Breastfeeding is not considered a risk factor for transmission of HBV to babies who have been vaccinated appropriately. Women may take tenofovir while breastfeeding.

Immunosuppression and Hepatitis B

HBV reactivation may occur during immunosuppressant therapy even in those with “cleared” infection. A separate NHS GGC guideline “Hep B Reactivation Guideline” is available on the intranet.

References

1. European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Management of chronic hepatitis B virus infection 2017. Journal of Hepatology 2017 vol. 67 j 370–398

2. Terrault NA *et al*. American Association for the study of Liver Disease (AASLD) Practice Guidelines for treatment of chronic hepatitis B. HEPATOLOGY, VOL. 67, NO. 4, 2018

3. Christian Schnier, Health Protection Scotland. Data presented September 13th 2012 at Royal College Physicians of Edinburgh.

4. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. Journal of Hepatology 2015 vol. 63 j 237–264

Appendix 1

IN CONFIDENCE

Please give this letter to the pharmacist when you hand in your prescription **HEPATITIS B TREATMENT** **INFORMATION FOR COMMUNITY PHARMACIST**	*提交您的药方时，请将此信交给药剂师* **乙型肝炎治疗** **为社区药剂师提供的信息**

This patient has been prescribed either tenofovir or entecavir for their hepatitis B infection and has selected your pharmacy as their preferred supplier

It is important that they have a continuous supply of their medication.

Community Pharmacies can order these drugs from suppliers

Supplies will generally be delivered the next working day if the order is placed before 4pm Monday to Friday. Please advise the patient when their completed prescription can be collected and particularly if a delay is anticipated

Appendix 2

Hepatitis B Interferon Treatment Schedule

Sticker

Consultant:

HIV Result / date:

On treatment monitoring. Results to be discussed at MDT after weeks 12 and 24. Refer back to medical clinic for review 3 months after completion of 48 weeks PEG treatment.

	Pre Rx	Week 12	Week 24	Week 48	6 month Post Rx	12 months Post
HBV DNA						
Quantitative Surface Antigen				[redacted]		
HBV e Antigen		[redacted]				
HBV e Antibody						

In addition, at each visit, check UE, LFT, FBC, Glucose. Check TFTs every 3 months:

Date								
Week No	**PTS**	**0**						
HB								
WCC								
Neuts								
Platelets								
ALT								
Bilirubin								
Glucose								
Creatinine								
Thyroxine TSH								
Weight								
Interferon Dose								
Dr Signature								
Comments								