NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Adult Hepatitis C Treatment Guideline

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.

Scottish Guidelines on the pretreatment assessment and on treatment monitoring for patients undergoing treatment with direct acting anti-virals (DAAs)

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Scope of this Guideline

This guideline gives guidance on the selection of patients for HCV treatment, pre-treatment assessment (including staging of liver disease), on treatment monitoring and post treatment care. Guidance on specific treatment regimens according to genotype, prior treatment status and disease severity should be sought from the Scottish National Hepatitis C treatment guidelines, which take in to account tendering by National Procurement Scotland and thus ensure that first line therapy choices provide best value to the NHS.

1. Who to Treat

All treatment-naïve and treatment-experienced patients, who are willing to be treated and who have no contraindications to treatment, should be considered for therapy irrespective of disease stage. This is in line with European Association for the Study of Liver disease guidelines, and the WHO elimination goals.

Contraindications are few. Those with limited life expectancy due to non liver co-morbidities are not appropriate for treatment. Other than this any patient, who wishes treatment, should be considered a candidate for treatment.

1.1. Drug and alcohol misuse.

Patients who drink to excess should be counselled regarding the risk to their liver and general health, and signposted to addictions services if not already engaged. A large study of patients in the veterans administration system concluded that unhealthy alcohol consumption (Audit C >4) was associated with a slight reduction in SVR, however SVR rates were good irrespective of Audit-C score, and excess alcohol should not preclude treatment (Tsui et al Drug and alcohol Dependence 2016). Patients who are drinking dependently may still be able to adhere to treatment, and this decision should be taken on a case by case basis by an experienced liver/ID nurse specialist, with discussion at MDT and consultant review if felt appropriate.

People who inject drugs (PWIDs) should be encouraged to have their HCV treated, with a view to preventing ongoing transmission and eradicating HCV before the development of more advanced fibrotic liver disease. Co-administration of DAAs with daily supervised opiate replacement therapy (ORT) allows for treatment success rates that are equivalent to other patients. Patients actively injecting but not on ORT should be encouraged to engage with the addiction team, and their ability to adhere to therapy judged on a case by case basis.

1.2. Elderly patients

Real world safety and efficacy amongst elderly patients does not differ from younger patients. Elderly patients should therefore be considered for treatment on the same basis as other patients. Given increasing evidence that SVR reduces mortality in patients without advanced chronic liver disease, together with the potential to lower cardiovascular risk, the absence of fibrosis should not be seen as a definite reason not to treat. A joint decision should be made with the patient.

1.3. Hepatitis B co-infected/exposed patients

HBsAg positive patients should be prophylactically treated with a nucleos(t)ide analogue, due the risk of reactivation during treatment, as per EASL and AASLD guidelines. HBsAg negative, anti-HBc positive patients should have their LFTs monitored during treatment, with HBV DNA testing in the event of an ALT flare (see below).

1.4. HIV co-infected patients

Patients with HIV/HCV co-infection have excellent SVR rates that do not differ from patients with HCV mono-infection. Drug-drug interactions with anti-retroviral therapy may require management, with input from the blood borne virus specialist pharmacist.

1.5 Patients developing HCV infection following receipt of a donor positive organ

These patients should initiate treatment within 3 to 10 days of receipt of a positive PCR result, as per the UK position statement. Treatment teams and transplant units should develop local protocols to ensure that the rapid treatment required is achieved.

1.6 Prioritisation of patients

The latest iteration of the National Clinical Guidelines for the treatment of HCV in adults (November 2017) no longer mandates prioritisation according to fibrosis severity, with treatment available to all. Given the increased risk of short term morbidity/mortality amongst patients with cirrhosis, individual centres should continue to ensure that patients with cirrhosis do not have unduly long waits to initiate treatment (<4 months recommended).

2. Pre-treatment work up

2.1. Confirmation of HCV status.

The majority of patients with a single positive result indicating active infection (positive HCV antigen or HCV PCR) will have chronic hepatitis C and should be worked up and proceed to treatment on this basis. The exception is the minority of patients with either a clearly defined recent time of acquisition (eg needlestick injury or symptomatic acute hepatitis C infection). Such patients may choose to wait until 6 months have elapsed (to satisfy the traditional definition of chronic hepatitis C and give the maximal chance for spontaneous clearance to occur). Alternatively treatment may be initiated if still positive at 3 months, at which time point the majority of patients who spontaneously clear will have done so. Such a decision should be taken in the context of the risk of such a patient being lost to follow up.

2.2. Liver disease co-factors:

An assessment of liver disease co-factors including alcohol and obesity will be obtained. Alcohol excess should be screened for using the FAST score. In addition the average number units of alcohol per week consumed should be recorded. Height and weight should be recorded and used to calculate BMI. Targeted lifestyle advice and/or signposting to addictions services should be carried out were appropriate.

A liver screen should be undertaken to include: Ferritin, Transferrin saturation, immunoglobulins, Anti-nuclear antibody, Liver autoantibodies (AMA/SMA), alpha-1-antitrypsin, and Caeruloplasmin (<50 years only).

2.3. BBV screen

All patients should have an up to date (within 6 months):

- HIV antigen/antibody screen
- HBsAg test
- anti-HBc antibody (does not require retested if previously positive).

In addition to the above, which are required for treatment, Vaccination for Influenza and Pneumococcus is advised for all patients with chronic liver disease. Anti-HBsAg antibody titres should be checked, and Hepatitis B vaccination should be recommended to the primary care provider if HBsAb is negative or if titre <100. Patients at risk of hepatitis A e.g. travel risk or MSM should have Hep A serology checked and vaccination advised if this is negative. Please refer to The Green Book for details.
https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book#the-green-book

2.4 HCV Genotyping/resistance testing.

HCV genotyping is now only required if knowing the genotype would change choice of drug regimen, and so can be omitted if it might inhibit the success of a treatment pathway. However genotyping is funded nationally and provides useful information on epidemiology and prognosis. A Genotype should be requested on all patients as part of the pre-treatment work up. However the absence of a genotype result does not preclude initiating treatment with a pan-genotypic regimen where the results are pending or have not been able to be performed, for example due to lab technical issues, insufficient or missing samples.

Baseline Ns5A resistance testing is currently funded as a "service to medicine" by MSD, for Genotype 1 patients. Its clinical utility is in deciding which GT1a patients with a high viral load (>800,000 iu/ml) require lengthening of Grazoprevir/Elbasvir treatment to 16 weeks with the addition of ribavirin, due to the presence of Elbasvir specific resistance associated variants (RASs).

Ns5A resistance testing should also be requested for the small number of patients who fail treatment with a DAA regimen. Ns3a resistance testing should also be requested for those patients who fail a regimen containing a protease inhibitor (paritaprevir/grazoprevir/pibrentasvir). Decisions on retreatment should be made following MDT/expert discussion.

2.5 Co-morbidities and concomitant medication:

A list of comorbid conditions should be obtained along with a list of the patient's regular and as required medications. They should also be asked about over the counter medications, herbal medications and recreational drugs. All identified medications should be screened against the www.Hep-Druginteractions.org website and any interactions identified appropriately managed, with input from the BBV specialist pharmacists if required. The importance of not starting new medication without confirming safety with the CNS should be reinforced to the patient and the patient's GP.

2.6 Pre-treatment discussion

Pre-treatment discussion should include the importance of adherence on achieving SVR12, and reinforcement of any specific dosing requirements (e.g. dosing with food). The importance of not discontinuing medication prematurely, due to the risk of resistance, should be stressed to the patient.
The importance of the SVR12 blood test in determining treatment success should be made at the initial assessment, and reinforced at all subsequent visits.

2.7 Assessment of fibrosis

There are several methods of fibrosis assessment one of which is fibroscan. The following cut offs are used to define different stages of liver disease:

- F4 ≥12.5 kPa (11.9 HIV co-infected)
- F3 ≥ 9.5 <12.5 kPa (8.8 HIV co-infected)
- F2 >6.9 <9.5 kPa (6.5 HIV co-infected)
- F0-1 ≤ 6.9 kPa (<6.5 HIV co-infected).

An alternative, and acceptable method of excluding advanced fibrosis is to use the patients AST, ALT, age and platelet count to calculate the FIB-4 score (https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis). Patients with a score <1.45 are highly unlikely to have advanced fibrosis and may be treated as non cirrhotic. Note that alcohol excess increases AST and lowers the platelet count, making false positives more likely in those drinking to excess. False positives are also more likely in those with HIV co-infection. Those patients with a score >1.45 require assessment with fibroscan.

Patients with a liver stiffness measurement (LSM) in the F3 range should have careful consideration as to their disease stage taking in to account LFTs, platelet count, stigmata of chronic liver disease, and ultrasound findings. Some patients with a LSM within the F3 range will have cirrhosis and a consultant decision (taking in to account the above factors) should be made about the probable disease stage. This is important with regards to defining the need for HCC surveillance post SVR (see below).

2.8 Review pre-treatment

Patients may be initiated directly onto treatment by nurse specialists according to local protocol arrangements or discussed at an MDT. Some patients may require a consultant review for the reasons outlined above (2.7), but this is not mandatory. Patients outside the agreed local protocols can proceed to treatment under nurse care following MDT discussion.

2.9 Work up of patients with advanced fibrosis

Patients with a fibroscan in the F3/F4 range require an ultrasound prior to commencing treatment. Patients with F0/2 disease do not, unless there are other concerns about their liver.

For patients who are attending other clinics, but failing recurrently to attend for ultrasound despite adequate counselling of its importance, then an individual consultant decision can be made regarding proceeding with treatment (following MDT discussion if appropriate). Most patients in this group will not have a cancer at the time of initiating treatment and the balance of risks to the patient is likely to favour proceeding with treatment, provided the team are satisfied that the patient's non compliance with ultrasound appointment will not preclude compliance with treatment. Patients with cirrhosis require an upper GI endoscopy to exclude the presence of varices unless they meet the Baveno criteria for non invasive exclusion of varices (LSM <20kPa and platelet count >150/mm3 (both performed within one year)).

2.10 Contraception

Female patients who are not post-menopausal and have not undergone sterilisation require counselling around contraception as below:

Non ribavirin containing regimens*:*	None of the DAAs have been tested in pregnancy, and patients should be counselled around the unknown risk to a child conceived during treatment. Pregnancy is not recommended. It should be documented that contraception has been discussed, and the method of contraception the patient is planning to use during treatment be documented. A pregnancy test should be performed prior to starting treatment.
Ribavirin containing regimens:	Ribavirin is highly teratogenic and effective contraception is mandatory. A negative pregnancy test should be obtained before commencing therapy. Couples, with one partner receiving treatment, should use two forms of contraception (as listed below) during treatment and for six months after treatment has ended. This conversation should be clearly documented and patients reminded of this at the end of treatment visit and the SVR12 visit.
Acceptable contraception includes:	• oral contraceptive pills (taking in to account potential drug-drug interactions) • contraceptive implant • male or female condoms • cap plus spermicide • intrauterine device (IUD)/intrauterine system (IUS) with hormone • abstinence during treatment.

2.11 Regimen specific considerations:

With regards to specific regimens, prescribers are expected to familiarise themselves with the summary of product characteristics (SPC) for regimens they prescribe, including any contraindications. Patients with advanced chronic liver disease (Child's B/C) should not be treated with a Ns3/4a protease inhibitor containing regimen (eg paritaprevir/grazoprevir/pibrentasvir), due to the substantially higher concentrations seen in these patients. A Child's calculation should be documented for all cirrhotic patients.

3. On treatment monitoring

There is no need to check a week 4 PCR. An end of treatment PCR can be obtained.
Separate guidance regarding monitoring of LFTs and Hb has been previously issued, and recently updated (see Appendix 1).
Patients who are on regimens that do not require monitoring of LFTs, but who are anti-HBc positive, should have LFTs checked at least once between week 4 and 8 of treatment (which may be end of treatment), and at the end of treatment. Such patients with an ongoing or worsening ALT elevation should have HBV DNA levels checked. The risk of reactivation amongst HBsAg negative, anti-HBc positive patients is low (<1%), however serious morbidity/mortality has been described.

4. Post treatment monitoring

A post treatment PCR should be taken at week 12 and/or 24 post treatment. For patients not attending for SVR12, all best effort should be made to obtain an SVR. If a patient repeatedly does not attend for SVR12 bloods despite a letter reinforcing the importance of these, then a letter to the patients GP (and/or CAT worker) asking them to check an HCV PCR. In addition a note should be entered on the front page of the patient's clinical record noting that "this patient has completed treatment for hepatitis C but not attended for bloods to ensure this has been successful. If they attend secondary care for any reason, please offer an HCV PCR blood test noting "post treatment" on the request.

5. Post SVR management:

All patients should be counselled that they should have at least annual BBV testing if they are engaging in activities with an ongoing risk of transmission. The risk of re-infection and the need for safe injecting practices (if relevant) should be discussed.

Patients with F0-2 disease should be counselled about any identified ongoing risk factors for liver disease (obesity and alcohol excess) and may be discharged.

Patients with F4 disease require ongoing follow up, with 6 monthly visits for bloods, clinical assessment and to schedule ultrasounds, for hepatoma surveillance.

Patients with F3 disease (note the importance of considering all information before assigning a patient to the F3 category – see pre-treatment fibrosis assessment above) should be assessed for risk factors for liver disease progression. Those with evidence of NAFLD or alcohol liver disease as co-factors should be considered for further follow up to assess for progression of liver disease.

5.1 Post SVR fibroscans

Liver stiffness does not accurately correspond to disease stage when prospectively evaluated with paired liver biopsies, and should not be used to ascertain regression of cirrhosis. At present no data supports the utility of post SVR fibroscan in ascertaining prognosis, though this may follow. It is not currently routinely recommended.

6. Relapse/reinfection

Relapsed HCV

Few patients will relapse, usually between end of treatment and week 12 SVR. These patients should be informed and a sample obtained to confirm relapse, test for resistance (see 2.4) and repeat the genotype.

A history should be taken to identify any possible risk behaviour that might indicate re-infection. The patient should be seen in a clinic to discuss the results and decide if relapse if likely and if so, when and what further treatment should be offered. Such patients should normally be discussed at the MDT.

A small number of patients will continue to take part in high risk behaviour and become reinfected. These patients are also very likely to be at higher risk of infecting others. For this reason it is reasonable to re-treat them with the appropriate first line (treatment naïve) regimen. Emphasis should be put on education around risk and where possible engagement with Addiction services. If re-infection is likely e.g. different GT, then the patient should be monitored for at least 3 months (see 2.1) to see if they achieve a spontaneous cure. If not they should be discussed at an MDT prior to commencing therapy.

Appendix 1: Guidelines for Monitoring HCV Therapy

Pre-treatment bloods

- HCV PCR (within 6 months of starting treatment)
- FBC, LFTs, U+Es, Coagulation, Liver screen
- BBV screen
  - HIV Antibody/Antigen (within 6 months of starting treatment)
  - HBsAg (within 6 months of starting treatment)
  - antiHBc antibody (does not require repeated if previous positive)

On-treatment monitoring

Additional monitoring is generally not required during treatment with DAAs. There are specific circumstances where additional monitoring is recommended.

Patients on RBV

- FBC, LFTs, U+Es at week 4, then 4 – 8 weekly intervals (or more frequently if dosage adjustments required)

Cirrhotic Patients

- Child-Pugh A - FBC, LFTs, U+Es at week 4, then at 4 – 8 weekly intervals
- Child-Pugh B/C - FBC, LFTs, U+Es at week 2 and 4, then at 4 weekly intervals

HBV co-infected (HBsAg +ve pts who should be treated prophylactically with a nucleotide analogue – see treatment guideline)

or HBV exposed (HBsAg –ve, anti-HBc +ve pts)

- LFTs at least once between week 4 and 8, and end of treatment.
- If ongoing/worsening ALT elevation – check HBV DNA

Patients with moderate-severe renal impairment (eGFR < 50 ml/min) on sofosbuvir-containing regimens

- U+Es every 4 weeks, with more frequent monitoring (1 – 2 weekly) if deterioration in eGFR <30 ml/min on treatment

Post-treatment bloods

- HCV PCR at end of treatment, 12 and/or 24 weeks post treatment

There may be situations where the frequency of monitoring may deviate from above, e.g. in the presence of significant drug interactions or co-morbidities

Naive/Experienced‡

‡excludes patients who have failed a Ns5a regimen (Daclatasvir, Elbasvir, Ledipasvir, Ombitasvir, Pibrentasvir, Velpatasvir) – see below

Genotype: _____

Genotype result not required to initiate treatment

Date of scan: __/__/____
Median LSM (IQR)
_____ (___)

F4 ☐ LSM ≥12.5kPa or decompensated ☐ (≥11.9 HIV)
F3 ☐ LSM ≥9.5 <12.5kPa (≥8.8 <11.9 HIV)
F2 ☐ LSM >6.9 <9.5 kPa (≥6.5 <8.8 HIV)
F0-1 ☐ LSM ≤6.9kPa (<6.5 HIV)
OR FIB-4 < 1.45 ☐

Surname:

Forename:

CHI:
(or addressograph label)

Non cirrhotic (F0-F3) & compensated (CPA) cirrhosis (F4)

- GT 1 or 4 → Grazoprevir/Elbasvir 12 weeks ☐
- GT 2, GT 3 or unknown → Glecaprevir/Pibrentasvir
  - Treatment naïve → 8 weeks ☐
  - Treatment experienced‡
    - GT 2
      - F0-F3 → 8 weeks ☐
      - F4 (CPA) → 12 weeks ☐
    - GT 3 or unknown → 16 weeks ☐

Decompensated cirrhosis (CPB/C) → 12 weeks ☐ Sofosbuvir/velpatasvir/ribavirin° → °Child's B: <75kg 1000mg, >75kg 1200mg; Child's C: 600mg, ↑ to wt based target as tolerated

Nurse prescriber, BBV pharmacist or Consultant confirmation of treatment plan/accuracy of info:
Name (Print):
Signature: _____
Date: ___/___/_____

Date of last HIV test: ___/___/_____
Pharmacy name:_____

Pharmacy Address:_____

Frequency/days of dispensing*:
_____
*eg daily supervised (Mon-Fri/Sat/Sun), weekly, fortnightly etc

Intended Start date†: ___/___/_____
†must be 4 weeks after addition to worklist
Contact Nurse:
Once above complete and scanned add patient to "Hep C pharmacy treatment request" shared worklist.

All other regimens require pre-authorisation from BBV pharmacist: ☐
Alternative regimen to be used: Indication:
‡ If prior Ns5A failure, then ensure resistance testing and MDT discussion: ☐
(consider repeat genotype, for those with risk factors for reinfection)

Pharmacy use:
Reviewed by:
Signature: Date:

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