Management of Hepatitis C

Background

Hepatitis C (HCV) is contracted by blood to blood contact. Sexual transmission is reported but is rare and probably by anal intercourse. Between 5 and 10% of patients develop an acute hepatitis, usually unnoticed, about six weeks from HCV exposure. Around 20% remain HCV RNA negative after exposure and are considered to have recovered, but there is no clear serological profile to indicate acquired immunity. 80% evolve to a chronic hepatitis, which is progressive rather than relapsing and remitting. 20% of the patients with chronic HCV develop cirrhosis within 1 to 3 decades. Risk factors for rapid progression are smoking, older age at the time of infection, high BMI, concomitant alcohol abuse, being male and HIV co-infection. Cirrhotic patients have a 25% risk of death in 5 to 10 years. The annual risk of HCC in HCV with cirrhosis is 3 to 5% and is rare in the absence of cirrhosis.

Who to test

The following groups should be tested for HCV:

- Blood/tissue donors
- Patients on haemodialysis
- Healthcare professionals who intend to pursue a career in a specialty that requires them to perform exposure prone procedures.

The following groups should be offered an HCV test:

- Patients with a persistently elevated alanine aminotransferase
- People with a history of injecting drug use
- People who are human immunodeficiency virus (HIV) positive
- Recipients of blood clotting factor concentrates prior to 1987
- Recipients of blood and blood components before September 1991 and organ/tissue transplants in the UK before 1992
- Children whose mother is known to be infected with HCV
- Healthcare professionals following percutaneous or mucous membrane exposure to blood which is, or is suspected to be, infected with HCV
- Prisoners
- People who originate from high prevalence populations
- People who have received medical or dental treatment in countries where HCV is common and infection control may be poor
- People who have had tattoos or body piercing in circumstances where infection control procedure is, or is suspected to be, suboptimal
- People who have had a sexual partner or household contact who is HCV infected

How to test and interpretation/management of results

1) Screening. A serum sample should be tested for anti-HCV antibody. A positive result demonstrates previous exposure or active infection.

2) Testing for active infection. If a screening test returns positive, a large EDTA sample should be sent to test for HCV RNA. A positive result indicates active infection. A negative result indicates clearance, which should be confirmed by repeat testing and no further action taken.

3) Workup for patients positive for HCV RNA. A full liver screen, HCV genotyping, HIV testing, HAV/HBV immunity assessment and an ultrasound scan to stage liver disease should be
undertaken preferably before referral to secondary care. The liver screen includes: hepatitis BsAg and anti-HBcore, liver autoantibodies, immunoglobulin profile, alpha-1 antitrypsin level, caeruloplasmin (if < 50 y o), ferritin, HBA1c, random glucose, LFT, AST, INR, UE and FBC.

**Hepatitis C treatment centres**

Usually, patients should be referred to their nearest treatment centre. These are:

- Addenbrooke's Hospital
- Basildon Hospital
- Bedford Hospital
- Ipswich Hospital
- Luton and Dunstable Hospital
- Norfolk and Norwich Hospital
- Peterborough Hospital

The other regional hospitals will be able to offer advice and workup for patients if they would like to be seen locally initially.

**Management of chronic infection**

Initial management of patients with chronic infection is liver disease staging. This is done by a combination of blood tests, ultrasound scan, elastography and liver biopsy. Liver biopsy is reserved for patients for whom there are either dual aetiologies or when definitive liver disease staging is required.

**Adult treatment**

Available treatment regimens are dictated centrally by NHS England and NICE. Regional prioritisation for therapy follows.

**Regional selection and prioritisation**

Patients are discussed at a multidisciplinary team meeting and if it felt that they are appropriate for therapy, will be prioritised according to the following guide:

1. Liver function. Patients with liver failure will receive top priority.
2. Liver disease stage. Patients with cirrhosis will be prioritised over patients with moderate fibrosis who will be prioritised over patients with mild fibrosis could be prioritised by Fibroscan score at the discretion of each treatment centre.
3. Medical co-morbidities. Examples include medical complications of hepatitis C, liver cancer, HIV and conditions that require immunosuppression such as liver transplantation.
4. Other hepatitis C associated complications
5. Infection risk to others
6. Patient being within a limited “treatment window”
7. Iatrogenic infection
8. Time on waiting list

**Blueteq, data collection and regional run rates**

For all patients being treated with direct acting antiviral therapies (DAAs), the following processes apply. **Blueteq forms** require completing, minimum datasets entered and treatment kept within the “run rate” stipulated by NHS England. The run rate is outside of the control of the treatment network (Operational Delivery Network [ODN]). It corresponds to the number of patients who may be treated with DAAs with time and has been distributed around the region based on capacity as follows.
Regional run rates

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Treatment regimens

There are multiple treatment regimens that are available through NHS England and NICE. Given budgetary constraints, NHS England stipulates that the following regimens are used. Second line therapy has to be approved by both Cambridge and Surrey central MDTs.
## First, second and third line DAA therapies from 01 04 18

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<td>12/16 (^1)</td>
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<td>All</td>
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<td>Sof/vel +/- riba</td>
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### Definitions

Decompensated cirrhosis - Childs Pugh B or C cirrhosis OR previous or on-going episode of decompensation (variceal bleed OR ascites OR encephalopathy) OR platelet count <50,000 per ml.

\(^1\) Patients with G1a or treatment experienced G4, high baseline viraemia (> 800,000) and/or previous null/partial response to interferon based therapy should receive 16/52 treatment with standard weight based ribavirin. Additionally, the choice of 16/52 duration for G1a is at MDT clinical discretion and factors

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such as NS5A resistance profile and patient’s ethnicity and gender may be taken into account. For 12/52 therapy without ribavirin otherwise.

2 24 weeks for previous null responders or those with low albumin or platelets. Abbvie regimen cannot be used for patients with decompensated cirrhosis.

3 16 weeks for patients who have previously failed peg/riba

4 See below

Abbvie 3D = ombitasvir/paritaprevir/ritonavir and dasbbuvir
Abbvie 2D = ombitasvir/paritaprevir/ritonavir

Previous PI therapy is not a contraindication to use of the Abbvie regimen (Poordad et al EASL 2016).

5 GT1a and GT1 without a subtype

6 Sof/vel/vox has been designated 5th line and its use would require ratification at the national MDT

Retreatment of DAA treatment failure

Patients without decompensated cirrhosis who have been compliant with DAA therapy and not re-infected are eligible for treatment with 12 weeks sof/vel/vox, which will not count towards the run rate.

Patients with decompensated cirrhosis or those at high risk of death without treatment may be retreated with 24 weeks sof/vel +/- riba. Full details may be found here. The most common exclusion criterion will be patients who have received 24 weeks retreatment already through the initial Early Access Programme. Allocation goes through the standard Blueteq pathway.

Definitions of advanced or decompensated cirrhosis

- Evidence of present or previous decompensated cirrhosis with an episode of ascites, variceal bleeding, or encephalopathy; OR
- Child Pugh Score ≥ or = 7; OR
- The patient is at significant risk of death or irreversible damage. For example, patient is currently listed for liver transplantation; OR
- The patient has biochemical or haematological indicators of advanced cirrhosis and/or significant portal hypertension eg albumin < 35, platelets < 50.

Follow up

For patients who are not cirrhotic and clear HCV RNA at week 12 (SVR12), follow up is recommended at week 48-60 for an HCV RNA to assess SVR48-60 and to restage liver disease (usually by blood tests and Fibroscan). If HCV RNA is negative and restaging reassuring then patients may be discharged. Exceptions to this are those with other significant risk factors for liver disease who may require long term follow up, or those with risk factors for acquisition of blood borne viruses who should continue in an appropriate screening programme through primary care or the drugs and alcohol service.

For patients with F4 fibrosis by Fibroscan before treatment whose elastography score regresses to < 12.5 kPa after treatment and in the absence of blood test or imaging evidence of cirrhosis, a reasonable approach is to either undertake liver biopsy staging to inform surveillance requirement or to continue with a surveillance programme.

As part of assessment of treatment efficacy, SVR48-60 is required. Standard sample letters to facilitate this are given at the end of these guidelines.

Surveillance/prevention

- 6-monthly ultrasound scanning is recommended for patients with severe fibrosis or cirrhosis for HCC. AFP can be assessed, but has a low specificity in HCV.
- A variceal surveillance programme is indicated for cirrhotic patients (but can reasonably be delayed until the development of thrombocytopenia and splenomegal)
- Cirrhotic patients should receive osteoporosis surveillance.
- Vaccination against HAV and HBV in unexposed individuals is reasonable.
Management of acute infection

Whilst interferon is still available for the treatment of acute infection, oral antiviral agents are much better tolerated and highly effective. Reasonable management is to wait for assessment of natural clearance (4 to 6 months). Then standard therapy can be used in the presence of chronic viraemia.

HIV/HCV co-infection

Staging and surveillance guidelines are as for chronic infection. Treatment decisions are similar, but IFN based regimens have poorer efficacy and progression to cirrhosis with co-infection is more rapid. DAA therapy has shown excellent results in clinical trials.

Given that HIV is a significant risk factor for HCV disease progression, it is reasonable to employ a low threshold for instigating HCV treatment. In terms of HIV/HCV treatment, the following guidelines based on CD4 count are helpful:

1) In the presence of co-infection, if CD4 count is < 350 x 10^6 cells/L then HIV therapy is recommended. If treatment for HCV is being instigated then HIV therapy should be established first.

2) If CD4 count is 350-500 x 10^6 cells/L and HCV treatment is required, HIV therapy should be instigated first.

3) If CD4 count is > 500 x 10^6 cells/L then HCV treatment can be instigated before HIV therapy is required.

HBV/HCV co-infection

Initial management is by assessing which disease is dominant. This should be treated first. Once the dominant virus has controlled, close observation is required as it may have been suppressing the other virus, which could then require treatment.

Paediatric treatment

NHS England is not supporting sofosbuvir use currently. A rate card is available on request, but in summary under current funding and licensing agreements:

Children > 12 years:

Genotype 1 or 4 - combination ledipasvir / sofosbuvir
Genotype 2, 3, 5 or 6 - no therapy available until post puberty

Children < 12 years:

No therapy available

Treatment cases should be discussed at the central MDT.
**Standard SVR48-60 letters**

*Patient letter:*
Please would you arrange to have a repeat hepatitis C RNA test taken through your General Practice and ring ..... when you have had it taken. With previous interferon based therapies we know that there was a small chance of viral recurrence after “successful” clearance (<5%), and the odds are probably similar for the therapy that you had. For this reason, we recommend a check at two years and three to five yearly thereafter. It should be possible to do all this through your General Practice.

Thank you for your engagement with this.

Kind regards.

Yours sincerely

cc GP – thank you for your help with this. A large EDTA sample is required for HCV RNA testing.

*GP letter:*
This patient has completed hepatitis C therapy. We need to ensure that the treatment has been successful, but he/she has unfortunately defaulted from follow up. We would be grateful if you would perform an HCV RNA viral load test (EDTA bottle) and forward the results to our secure email address add. tr.hepatitis@nhs.net. Alternatively we could arrange testing at Addenbrooke’s at your/the patient’s request.

Thank you for your help with our mutual patient.

Yours sincerely