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 or snorting 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, body piercing or Botox 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.
**Quarterly regional run rates**

<table>
<thead>
<tr>
<th>Trust</th>
<th>Run rate to year end</th>
<th>Dec 19 – Jan 20</th>
<th>Feb 20-Mar 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basildon</td>
<td>57</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Bedford</td>
<td>42</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Cambridge</td>
<td>76</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Ipswich</td>
<td>30</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Luton</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Norwich</td>
<td>88</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Peterborough</td>
<td>58</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>371</strong></td>
<td><strong>186</strong></td>
<td><strong>185</strong></td>
</tr>
</tbody>
</table>

**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 the Cambridge MDT, otherwise treatment decisions should be ratified by the local MDT. The treatment proportions should be allocated according to the NHS England procurement deal, which is available for ODN members on request.

**Retrospective ratification process**

To avoid treatment delay for patients with uncomplicated hepatitis C and no significant drug interactions, it is reasonable practice to start patients on hepatitis C treatment with the following regimens and ratify that decision retrospectively at MDT.

- Genotype 1 and 4: elb/grz for 12 weeks
- Genotype 2 and 3: sof/vel for 12 weeks
- Pangenotypic: as part of agreed elimination initiative

**Genotype: unknown**

If it is not possible to obtain a genotype for a patient then the following regimens are approved:

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>1A</th>
<th>1B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cirrhotic and compensated cirrhotic</td>
<td>Sof/Vel 12</td>
<td>Gle/Pib 8</td>
</tr>
<tr>
<td>Decompensated cirrhotic</td>
<td>Sof/Vel +/- riba</td>
<td></td>
</tr>
</tbody>
</table>
### Genotype: known

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genotype</th>
<th>SubCond</th>
<th>Treatment History</th>
<th>Treatment History</th>
<th>Treatment (weeks)</th>
<th>Treatment (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1A</td>
<td>1B</td>
<td>1C</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

**GT1&4 Non Cirrhotic & Compensated Cirrhotic**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genotype</th>
<th>SubCond</th>
<th>Treatment History</th>
<th>Treatment (weeks)</th>
<th>Treatment (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (not 1b)</td>
<td>1 (not 1b)</td>
<td>n/a</td>
<td>Naïve</td>
<td>Elb/Grz</td>
<td>Sof/Led (8^4/12)</td>
</tr>
<tr>
<td>Non Cirrhotic</td>
<td>Non Cirrhotic</td>
<td>n/a</td>
<td>Pre treated</td>
<td>Sof/Led (8^4/12)</td>
<td>Gleich/Pib (8)</td>
</tr>
<tr>
<td>1b</td>
<td>1b</td>
<td>n/a</td>
<td>Naïve</td>
<td>Pre treated</td>
<td>Elb/Grz</td>
</tr>
<tr>
<td>Non Cirrhotic</td>
<td>Non Cirrhotic</td>
<td>n/a</td>
<td>Naïve</td>
<td>Elb/Grz</td>
<td>Sof/Led (12)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>n/a</td>
<td>Naïve</td>
<td>Elb/Grz</td>
<td>Sof/Led (12)</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>1 (not 1b)</td>
<td>Comp</td>
<td>All</td>
<td>Elb/Grz</td>
<td>Sof/Led + R (12)</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>1b</td>
<td>Comp</td>
<td>All</td>
<td>Elb/Grz</td>
<td>Sof/Led + R (12)</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>4</td>
<td>Comp</td>
<td>All</td>
<td>Elb/Grz</td>
<td>Sof/Led + R (12)</td>
</tr>
</tbody>
</table>

**GT2,3,5&6 Non Cirrhotic & Compensated Cirrhotic**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genotype</th>
<th>SubCond</th>
<th>Treatment History</th>
<th>Treatment History</th>
<th>Treatment (weeks)</th>
<th>Treatment (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
<td>n/a</td>
<td>Naïve</td>
<td>Sof/Vel (12)</td>
<td>Gle/Pib (8)</td>
<td>N/A</td>
</tr>
<tr>
<td>Non Cirrhotic</td>
<td>Non Cirrhotic</td>
<td>n/a</td>
<td>Pre treated</td>
<td>Naïve</td>
<td>Sof/Vel (12)</td>
<td>Gle/Pib (8)</td>
</tr>
<tr>
<td>3</td>
<td>n/a</td>
<td>Naïve</td>
<td>Sof/Vel (12)</td>
<td>Gle/Pib (8)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Non Cirrhotic</td>
<td>Non Cirrhotic</td>
<td>n/a</td>
<td>Pre treated</td>
<td>Naïve</td>
<td>Sof/Vel (12)</td>
<td>Gle/Pib (8)</td>
</tr>
<tr>
<td>5/6</td>
<td>All</td>
<td>Naïve</td>
<td>Sof/Vel (12)</td>
<td>Gle/Pib (8)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>2</td>
<td>Comp</td>
<td>All</td>
<td>Sof/Vel (12)</td>
<td>Gle/Pib (8/12^2)</td>
<td>N/A</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>3</td>
<td>Comp</td>
<td>All</td>
<td>Sof/Vel +/- R (12)</td>
<td>Gle/Pib (12/16^2)</td>
<td>N/A</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>5/6</td>
<td>Comp</td>
<td>All</td>
<td>Sof/Vel (12)</td>
<td>Gle/Pib (8/12^2)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**GT1-6 Decompensated Cirrhotic**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genotype</th>
<th>SubCond</th>
<th>Treatment History</th>
<th>Treatment History</th>
<th>Treatment (weeks)</th>
<th>Treatment (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (not 1b)</td>
<td>Decomp^3</td>
<td>All</td>
<td>Sof/Led + R (12)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>1b</td>
<td>Decomp^3</td>
<td>All</td>
<td>Sof/Led + R (12)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>2</td>
<td>Decomp^3</td>
<td>All</td>
<td>Sof/Led + R (12)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>3</td>
<td>Decomp^3</td>
<td>All</td>
<td>Sof/Led + R (12)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>4</td>
<td>Decomp^3</td>
<td>All</td>
<td>Sof/Led + R (12)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>5/6</td>
<td>Decomp^3</td>
<td>All</td>
<td>Sof/Led + R (12)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Definitions

1. 12 weeks for all patients is recommended. If viral load and genotyping data are available then clinicians may wish to consider increasing the duration of treatment to 16 weeks and adding in ribavirin for patients with G1a, high viraemia (>800,000) and/or NS5A RAVs

2. Patients who have been pre-treated with PI +/- sofosbuvir +/- ribavirin 12 weeks therapy is recommended for GT 1,2,4,5,6 and 16 weeks for GT3

3. Decomp cirrhosis is defined as those with Childs-Pugh B or C cirrhosis, OR patients with on-going or previous, recovered episode of decompensation OR patients with a platelet count of <50,000 5.Gle/Pib for Compensated Cirrhotics only

4. 8 weeks therapy is recommended for GT1 Naive patients , 12 weeks therapy is recommended for GT1 Pre-treated patients

Note: For patients pre-treated with DAA's alternative policies apply

Retreatment: see below
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. 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.

Retreatment of reinfection

Treatment of reinfection was commissioned from 17 September 2019. Given that the infection is new, first choice therapy should be used (not sof/vel/vox). Counselling regarding measures to prevent reinfection must be undertaken before starting and during treatment.

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 splenomegaly).
- Cirrhotic patients should receive osteoporosis surveillance.
- Vaccination against HAV and HBV in unexposed individuals is reasonable.

Management of acute infection

DAA treatment is commissioned by NHS England, which includes use for recipient infection from HCV positive solid organ donation.

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. Treatment cases should be discussed at the central MDT. A rate card is available on request, but in summary first line treatment under current funding and licensing agreements:

**Children > 12 years:**

Genotype 1 or 4 - combination ledipasvir / sofosbuvir  
Genotype 2, 3, 5 or 6 - glecaprevir/pibrentasvir  
Decomp cirrhosis - sof/led and sof/vel are available

**Children < 12 years:**

No therapy available