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.

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

<table>
<thead>
<tr>
<th>Trust</th>
<th>Feb March</th>
<th>April May</th>
<th>June July</th>
<th>Aug Sep</th>
<th>Oct Nov</th>
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<tbody>
<tr>
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<td>11</td>
<td>11</td>
<td>TBC</td>
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<td>Bedford</td>
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<tr>
<td>Luton</td>
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<td>17</td>
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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 Oxford central MDTs.
## First and second line DAA therapies

<table>
<thead>
<tr>
<th>Genotype, stage and treatment history</th>
<th>Lowest acquisition cost therapy</th>
<th>Second line</th>
<th>Third line</th>
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<tr>
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<td>Treatment</td>
<td>Wks</td>
<td>Treatment</td>
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<td>12/16*</td>
<td><strong>Sof/led</strong></td>
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<tr>
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<td>Pre treated</td>
<td>12/16*</td>
<td><strong>Sof/led</strong></td>
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<td><strong>Naive</strong></td>
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<td>Pre treated</td>
<td>12</td>
<td><strong>Sof/led</strong></td>
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<td><strong>Naive</strong></td>
<td>12</td>
<td><strong>Sof/vel</strong></td>
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<td><strong>Naive and IFN contra-indicated</strong></td>
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<td><strong>Sof/vel</strong></td>
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<td></td>
<td><strong>Naive &lt; F3 fibrosis</strong></td>
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<td><strong>Pre treated</strong></td>
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<td><strong>Sof/vel</strong></td>
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<td><strong>Sof/vel</strong></td>
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<td><strong>5</strong> All</td>
<td>12</td>
<td><strong>Sof/vel</strong></td>
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<td></td>
<td><strong>6</strong> All</td>
<td>12</td>
<td><strong>Sof/vel</strong></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.

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

For a DDI to qualify there should be no other viable treatment alternative that is ritonavir compatible

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

Abbvie 3D = Ombitasvir/Paritaprevir/ritonavir and Dasbuvir
Abbvie 2D = Ombitasvir/Paritaprevir/ritonavir
Previous PI therapy is not a contraindication to use of the Abbvie regimen (Poordad et al EASL 2016).

**Peg-IFN and ribavirin (PR) schedules for genotype 2**

**16 weeks** is a reasonable option for patients with an RVR, low pre-treatment viral load and in the absence of negative predictors of SVR.

**24 weeks** is recommended for patients with EVR.

**48 weeks** is recommended for patients with a $> 2$ log drop in viral load at week 12 and delayed virological response (DVR - RNA negative at week 24). It should also be considered for patients with an EVR and significant liver fibrosis.

**Stopping rules**

Treatment should be stopped for patients with $< 2$ log drop in viral load at week 12 or those with a partial response (detectable HCV RNA at weeks 12 or 24).

**Retreatment**

There is an Early Access Programme for use of glecaprevir and pibrentasvir for patients with compensated (Child Pugh A) cirrhosis in the following categories:

- GT 1, 4, 5 or 6-infected patients previously treated with NS5A inhibitors
- GT 2, 3, 5 or 6-infected patients and with chronic kidney disease (stage 4 and 5)
- GT 3-infected patients previously treated with peg-interferon, ribavirin, and/or sofosbuvir

Patients who satisfy these criteria should be discussed in the central MDT.

**Follow up**

For patients who are not cirrhotic and clear HCV RNA at week 12 (SVR12), follow up is recommended 6 monthly for two years. Discharge with 3-5 yearly HCV RNA general practice checks is reasonable thereafter. Exceptions to this are patients with other significant risk factors for liver disease or those with progressive fibrosis by elastography or other accepted criteria.

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.

**Definitions of interferon ineligibility**

Some patients are ineligible for interferon. Criteria for this follow.

**Absolute criteria**

1. Patients who have had to stop IFN previously due to side effects
2. Significant autoimmune disorder
3. Hypersensitivity to PEG or any of its components
4. Decompensated hepatic disease
5. Major uncontrolled depressive illness
6. A baseline neutrophil count below 1500/$\mu$L, a baseline platelet count below 50,000/$\mu$L or baseline haemoglobin below 10 g/dL (if uncorrectable)
7. Pregnancy
8. Uncontrolled epilepsy

**Relative criteria**
1. Organ transplantation
2. Other psychiatric disorder
3. Retinopathy
4. A history of pre-existing cardiac disease
5. Clozapine
6. Other

**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**

Efficacy of pegylated IFN based regimens is high in patients with acute HCV infection. It is reasonable to wait until 12 weeks after identification of infection to treat, as at least 20% will clear the virus. After 12/52, patients with persistent viraemia should consider treatment as efficacy is high at this stage of the disease. Genotype specific regimens should be employed, although there are few data to base this recommendation on.

**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.
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.uk. 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