A meeting of the network was held on 11 April 2008 at which the current evidence base for hepatitis C treatment was reviewed. These guidelines have been produced as a result of that meeting for use by Network members.

The document is divided into 3 sections:

1. Definitions and agreed testing protocols
2. Treatment protocols
3. Grey areas where cases may need discussing on an individual basis.

The guidance is intended to be of use to Network members but is not all inclusive and cannot cover all areas in the field of hepatitis C. Local expertise should be consulted for difficult-to-manage patients where guidelines cannot be written. The treatment and appropriate monitoring of patients with chronic hepatitis C remains the responsibility of the clinician managing that patient and individual patient factors will often have to be taken into consideration.

All network members are reminded that some guidance is outside current NICE guidance for hepatitis C treatment and some recommendations include “off-label” use of the drugs we all use for treatment. Viral load definitions also differ from licensed definitions but are generally more conservative, and treatment duration especially in short course treatments also differ. The network has not been prescriptive about which products should be used - this is left to the discretion of the prescriber but the licensing indications are listed below for information.

1. **Roche Products**

Licensed for short course treatments for genotypes 1, 2 and 3. Definition of low viral load <800000 copies/ml. Not licensed for re-treatment after failure of standard course treatments at time of writing. Not licensed for 72 week treatment in genotype 1.

2. **Schering Plough products**

Licensed for short course treatments for genotype 1 but not 2 or 3. Definition of low viral load <600000 copies/ml. Licensed for re-treatment after failure of standard course treatments. Not licenced for 72 week treatment in genotype 1 at time of writing.
1. Definitions and agreed testing protocols

The following terms are referred to within this document and are defined below:

1. Standard treatment
2. Short course treatment
3. Long course treatment
4. Definitions of viral response

Standard treatment

These are the treatment durations recommended by NICE and include 48 week protocols for genotype 1 (genotype 4,5,6 to be included here) and 24 week protocols for genotype 2 and 3.

Short course treatments

These apply to genotype 1, 2 and 3 infection. Data on genotype 4-6 are too limited and patients should be treated for 48 weeks using the NICE recommended guidelines for genotype 1 - ie check quantitative PCR at 12 weeks and continue only if negative or 2 log drop. We suggest checking PCR at 24 weeks also and if it has risen on treatment at this stage stop therapy.

Short course is defined as treatment duration shorter than that currently recommended by NICE ie shorter than 24 weeks for genotypes 2 and 3 and shorter than 48 weeks for genotype 1. Suitable patients are identified by their baseline quantitative PCR and by the rapidity of their viral response as determined by a week 4 PCR (rapid viral response - see below). They must also not have any of the exclusion criteria (see below). The network recognised that this practice was outside NICE recommendations and would therefore be audited region-wide in an audit led by Jacqui Smithson and Peter Moss (Hull).

In all 3 of these genotypes there is the possibility for crossover into the standard treatment duration arm if the week 4 PCR is not encouraging.

Patients who relapse within 6 months of finishing short course treatments should be offered standard length re-treatment.

Exclusions for short course treatments

We have considered the following patients are not suitable for short course treatment:

- Cirrhotic patients (Stage 5 and 6 if histology known)
- Coinfected patients (HIV or HBV)
- Patients with platelet counts less than 140 (surrogate marker for fibrosis), unless there is a known alternative cause for thrombocytopenia e.g. ITP in which short course treatment may be considered a safer alternative provided selection criteria are met.
- Patients with BMI greater than 27
- Patients older than 45 years
Patients on long-term immunosuppression eg azathioprine etc.

**Long course treatment**
Currently refers to 72 week treatment for slow viral responders (see below) with genotype 1 infection.

**Definitions of viral response**
Rapid virological response (RVR)
- Undetectable HCV RNA levels at week 4

Early virological response (EVR)
- $\geq 2 \log_{10}$ drop in HCV RNA at week 12

Slow virological response
- HCV RNA positive at weeks 4 and 12, negative at week 24

End-of-treatment response (EOT)
- Undetectable HCV RNA levels at end of treatment
  (24 weeks for HCV genotype 2/3, 48 weeks for HCV genotype 1)

Sustained virological response (SVR)
- Undetectable HCV RNA levels at end of treatment and follow-up (24 weeks post-treatment)

Patients who are negative at end of treatment are **end of treatment responders**
Patients who are positive at end of treatment are **end of treatment non-responders**
Patients who are negative at end of treatment but become positive at 6 months are **responder-relapsers**
Patients who are negative at end of treatment and remain negative 6 months after end of treatment have **sustained viral response**
Positive end of treatment PCRs may be indication for longer course pathway – see individual protocols.
PCR Testing Protocols - all treatment protocols/duration

For audit purposes to ensure uniform data could be collected we agreed that PCR testing would be carried out as follows:

Baseline PCR
- All patients - should be done at start of treatment
  - To determine genotype and viral load

Week 4 PCR
- All patients
  - Decision making for short course patients in genotype 1, 2, 3
  - Will allow comparison data

Week 12 PCR
- All patients
  - Decision making for genotype 1 patients not on short course pathway, or those on short course pathway who need switching to standard course.
  - End of treatment PCR for genotype 2/3 patients in short course pathway
  - Aids decision making about retreatment and slow virological response

Week 24 PCR
- For patients still on treatment
  - End of treatment for short course genotype 1
  - Stopping decision for standard 48 week course genotype 1
  - End of treatment for standard course genotype 2+3

Week 48 PCR
- For standard course genotype 1 patients still on treatment
  - End of treatment PCR

Any longer treatment duration - suggest PCR checked 3 monthly - if rising - stop.

All patients have end of treatment PCR.

All patients have PCR checked 6 months after end of successful therapy (sustained viral response)

WEYHN Chronic hepatitis C treatment guidance.doc
Discharge in Sustained viral response patients

If this is achieved patients can be discharged back to their GPs if at early stages. At SJUH we continue to keep Ishak stage 5 and 6 patients under 6 monthly review for cirrhosis monitoring.

2. Treatment Algorithms

Genotype 1
Genotype 2
Genotype 3
Algorithm for Genotype 1 patients

Genotype 1
Check baseline PCR

<400 000 iu/ml
(low viral load)

Suitable for short course
Check exclusion criteria

<400 000 iu/ml
(low viral load)

<400 000 iu/ml
(low viral load)

Suitable for short course
Check exclusion criteria

>400 000 iu/ml
(high viral load)

Not suitable for short course

>400 000 iu/ml
(high viral load)

>400 000 iu/ml
(high viral load)

If excluded

Negative

Positive

Negative

Positive

Negative

Positive

Negative

Positive

Week 24 PCR
End of treatment

Stop treatment

Week 4 PCR

Negative

Week 12 PCR

Week 4 PCR
(audit data)

Week 24 PCR

Stop treatment

PCR negative or >2 log drop

Week 24 PCR

PCR positive or <2 log drop

PCRs negative or >2 log drop from baseline continue as per standard treatment arm. If not - stop.

PCR check 6 months after end of treatment to determine SVR in patients who were PCR negative at end of treatment

If negative discharge to GP (unless stage 5/6-cirrhotic)

If PCR positive and received short course, re-treat along high viral load pathway

*see guidance on potential for 72 week treatment
Algorithm for Genotype 2 Patients

1. **Genotype 2**
   - **Week 4 PCR**
     - **Negative**
       - **Suitable for short course**
       - **12week**
         - **Negative**
           - **End of treatment**
           - **Stop treatment**
         - **Positive**
           - **If excluded**
     - **Positive**
       - **12 week PCR**
         - **(audit, long treatment)**
         - **Treat for 24 weeks**
         - **Week 24 PCR**

**PCR check 6 months after end of treatment to determine SVR in patients who were PCR negative at end of treatment**

- **If negative discharge, (unless stage 5/6 - cirrhotic)**
- **If PCR positive and received short course, retreat for 24 weeks**
**Algorithm for Genotype 3 Patients**

- **Baseline PCR**
  - **<600,000 iu/ml (Low viral load)**
    - Suitable for short course
    - **Week 4 PCR**
      - **Negative**
        - Stop treatment
      - **Positive**
        - **Week 12 PCR**
          - **Negative**
            - End of treatment
          - **Positive**
            - (failed short)
  - **>600,000 iu/ml (High viral load)**
    - **Week 4 PCR**
    - **Week 12 PCR**
      - **Positive**
        - Treat for 24 weeks
      - **Negative**
        - If excluded
          - Stop treatment
        - **Week 24 PCR**
          - PCR check 6 months after end of treatment to determine SVR in patients who were PCR negative at end of treatment
            - If negative discharge (unless stage 5/6 - cirrhotic)
            - If PCR positive and received short course, retreat for 24 weeks
3. “Grey” areas

- 72 week treatment in genotype 1 patients
- Retreatment
- Genotype 4,5,6
- HIV co-infection
- HBV co-infection
- Supportive therapy
- Renal failure

72 Week Treatment Protocol for Slow Responders with Genotype 1

Some patients with genotype 1 infection may respond to prolonged courses of combination therapy. These would be the slow viral responders.

Definition of slow virological response

- HCV RNA positive at weeks 4 and 12, negative at week 24

The WYHN did not agree a firm recommendation on this but there will be patients that may want it and which units wish to consider. We suggest therefore:

- Such patients should be considered on an individual basis.
- The decision to continue should ideally take place in a multidisciplinary setting.
- There should be a documented discussion of the benefit and risk of prolonging therapy with the patient.

If there have been severe side effects or the need for supportive additional medication during the standard treatment length then long treatment should not be considered.

Additional therapy may include

- Thyroxine/ anti-thyroid drugs
- Anti-depressant medication started during therapy
- The need for blood products, erythropoietin of G-CSF during treatment

The following patients would meet criteria for 72 week therapy:

- Patients who have detectable, but > 2 log drop, in PCR at 12 weeks with undetectable PCR at 24 weeks.

These patients are slow responders

The decision can therefore be made before the end of standard treatment for genotype 1 patients based on the 24 week PCR.
It is probably more cost effective to have the conversation and decision making discussions before end of treatment than to end treatment and then retreat at a later date.

Recheck PCR at 12 weekly intervals: if PCR becomes detectable, stop treatment.

**Retreatment**

This is a controversial area at present.

NICE guidelines state the following patients are suitable for retreatment:

- If they received interferon alfa (non-pegylated) as part of monotherapy or combination therapy) but remain PCR positive.
- If they received pegylated interferon monotherapy only and were non-responders or responder-relapsers.

At SJUH we are generally following NICE guidance on retreatment.

However the term “retreatment” implies that patients have received standard duration treatment for Hepatitis C before.

Therefore patients undergoing *short course treatment* who are end of treatment non-responders or responder-relapsers should be offered retreatment along standard duration pathways.

**Retreatment after standard course therapy**

The other possibilities for retreatment are starting to emerge in the literature and a licence has been recently granted for retreatment in circumstances differing from the current NICE guidance. The data so far suggests it may benefit patients falling into the *responder-relapser group* ie PCR negative at end of treatment who become positive within 6 months and therefore do not achieve a SVR.

Retreatment involves commencing this group back on combination therapy (only pegylated interferon alfa-2b has this licence, and it involves weight based Peg-IFN and ribavirin dosing) and checking the week 12 PCR which must be completely negative to continue for a total of 48 weeks. It makes sense to check the PCR at 24 weeks because there is no point continuing if it becomes positive again on treatment, but by definition of patient selection the chances of this should be very small.

Reported results are that overall 37% will get through the negative week 12 PCR requirement, and of those 57% will achieve a SVR. (Overall therefore this looks like chances of achieving a SVR at start of retreatment equate to about 25%).

In genotype 1 patients 29% achieve a negative week 12 PCR and of those 48% achieve a SVR. In genotype 2 patients the figures are 77% and 74% respectively and in genotype 3 the figures are 79% and 72% respectively. Adding fibrosis into the mix brings the figures down if advanced but the data has not been subdivided into genotype. For example a cirrhotic patient has around a 30% chance of getting through the week 12 stage, and after that a 46% chance of responding.

Therefore it may be worth opting for 72 week treatment in genotype 1 patients who look like they are slow responders but opting to retreat genotype 2 and 3 patients who are responder-relapsers after standard...
treatment courses. Cirrhotic patients look less cost effective in this group if judging by SVR rates alone but the consequences of a small chance of success have obvious benefits.

Retreatment is left to the discretion of the treating teams.

Other areas

- **Genotype 4,5,6**
  Data probably not sufficient yet to apply short/long course strategies. Stick to standard duration therapy along genotype 1 pathway.

- **HIV and HBV co-infection**
  HIV co-infection should be treated as per the APRICOT trial data (pegylated interferon alfa 2a) - essentially the genotype 1 standard treatment duration pathway - until further data becomes available. Data from the CRESPO trial (pegylated interferon alfa 2b) is also available. All genotypes therefore follow standard course genotype 1 pathway.
  
  HBV co-infection should be managed as per HCV mono-infection except that the pegylated interferon should be continued for 48 weeks, if the HBV meets criteria for treatment as per regional guidelines. If the patient has cirrhosis the danger of a flare of hepatitis B causing decompensation needs to be taken into account and if thought to be unreasonable then the hepatitis B should be managed alone according to regional hepatitis B guidelines.

- **Supportive treatment**
  There is no guidance on the use of erythropoietin/blood transfusion and G-CSF to support patients through the side-effects of treatment. Both are expensive and the benefit of treatment must be considered carefully. Their use tends to be higher in patients with cirrhosis. SJUH Liver Unit has departmental guidelines outside the scope of this document but the Liver Unit hepatologists or pharmacist should be able to advise where necessary. Management of thrombocytopenia also needs consideration on a case by case basis.

- **Renal failure**
  A difficult area and worth discussing on a case by case basis. Look out for license restrictions (Roche is licensed for combination therapy in renal failure at reduced doses, SP is only licenced for monotherapy when Creatinine clearance <50).

**Guidance:**


For WYHN, later renamed WEYHN. Review overdue at 2012.