Guidelines for Laboratory Testing of Patients with hepatitis C in Greater Manchester

Author: PE Klapper on behalf of the Laboratory Consultative Group
These Guidelines should be read in conjunction with the ‘Treatment Guidance for Patients with hepatitis C in Greater Manchester’ issued 5th August 2009. The Guidance refers to virological testing of patients and does not detail biochemical, haematological or histopathological testing of patients with hepatitis C.

Definitions of responses to treatment

**Sustained viral response (SVR)**
Undetectable levels of hepatitis C RNA* (PCR) on blood testing 6 months after completion of antiviral therapy. This is the ultimate aim of therapy as it is associated with long term remission from active infection and marked reduction in the frequency of complications of liver failure and hepatocellular carcinoma.

**End-of treatment response (ETR)**
Undetectable levels of hepatitis C RNA on blood testing at the end of planned treatment.

**Primary non-responder**
A patient who fails to achieve an end of treatment response, or in whom treatment is stopped early because to early blood tests show failure of viral suppression below pre-determined values that predict failure of response.

**Responder-relapser**
A patient who achieves an end-of treatment response but has recurrence of detectable virus six-months after treatment cessation.

**Early viral response (EVR)**
A 2-log or greater reduction in viral levels 12 weeks after starting treatment. EVRs may be classed as complete (negative PCR at week 12 – cEVR) or incomplete (positive PCR but viral load shows greater than 2 log reduction from pre-treatment levels – iEVR).

**Rapid viral response (RVR)**
Undetectable levels of hepatitis C RNA 4 weeks after starting treatment.

**Sample dilution**
Undetectable levels of HCV RNA are reported as HCV RNA NOT detected (<30 iu/ml: log iu/ml = <1.48). The HCV RNA test requires a minimum volume of 1.5ml serum or plasma if this volume is not available to test a 1/10 dilution of the sample is made in HCV RNA negative plasma before the test is performed. This reduces the test sensitivity slightly. Positive samples will be reported after the quantity of HCV RNA has been corrected for the dilution factor negative samples will be reported as: HCV RNA NOT detected (<300 iu/ml: log iu/ml = <2.48).
HCV PCR may be performed on either serum samples or plasma samples.

1Initial screening by HCV PCR may use either qualitative or quantitative HCV PCR tests.
Diagnosis of Hepatitis C
Non-healthcare settings on people with poor venal access

**HCV antibody dried blood spot test**

- **- ve**
  - **no further action**
  - Report as: “HCV antibody not detected by dried blood spot testing”

- **+ ve**
  - **confirmatory HCV antibody test**
  - **- ve**
    - **monitor liver enzymes repeat HCV PCR at 12 months**
      - Report as: “HCV antibody DETECTED by dried blood spot testing; Consistent with HCV infection at some time. Suggest monitor liver enzymes over 12 months and repeat investigation in 12 months to confirm virus clearance”
  - **+ ve**
    - **HCV PCR & HCV genotype**
      - **- ve**
        - **refer for assessment**
          - Report as: “HCV antibody DETECTED by dried blood spot testing; Consistent with HCV infection at some time. Suggest monitor liver enzymes over 12 months and repeat investigation in 12 months to confirm virus clearance”
      - **+ ve**
        - **refer for assessment**
          - Report as: “HCV antibody DETECTED by dried blood spot testing; Consistent with HCV infection at some time. Suggest monitor liver enzymes over 12 months and repeat investigation in 12 months to confirm virus clearance”

1 Oral fluid testing is an alternative to dried blood spot testing but is not recommended. Oral fluid testing has lower sensitivity and specificity for detection of HCV antibody and has very poor sensitivity for detection of HCV RNA.

2 The dried blood spot test combines RNA detection and genotype identification.

3 Referral for assessment is assessment for suitability for treatment and may include initial referral for psychological assessment, help with drink addiction or substance misuse addiction.

Guidelines for Laboratory Testing of Patients with Hepatitis C in Greater Manchester
Diagnosis of Hepatitis C
Antenatal screening

HCV antibody test

- HCV antibody test & antigen combination test
  - + ve
    - HCV antigen and antibody not detected

- - ve
  - Referral for assessment
    - Consistent with active hepatitis C virus infection. Needs referral for consideration of treatment as outlined in local care pathway. Baby should be followed up in accordance with National Guidelines (see: Arch Dis Child 2006; 91:781-785). Test at 2-3 months for HCV RNA

- + ve
  - HCV RNA not detected. Consistent with HCV infection at some time. Suggest monitor liver enzymes over 6 months and repeat investigation in 6 months to confirm virus clearance; Baby should be followed up in accordance with National Guidelines (see: Arch Dis Child 2006; 91:781-785). Test at 2-3 months for HCV RNA

- - ve
  - Monitor liver enzymes. Repeat HCV PCR at 12 months

HCV PCR

- - ve
  - Report as: “HCV antigen and antibody not detected”

- + ve
  - Report as: “HCV antigen and antibody not detected”

1 Note: antenatal screening for HCV infection is only applied selectively, usually to those with a past history of intravenous drug abuse
Diagnosis of Hepatitis C
Screening of babies Under 12 months born to HCV infected mothers

At 8-12 weeks Hepatitis C PCR
- ve
Report as:
“HCV RNA not detected; HCV infection is unlikely but advise repeat investigation in 6-12 months”

- ve
Report as:
“HCV RNA not detected; HCV infection is unlikely but advise repeat test at 12-18 months for HCV antibody”

- ve
Report as:
“HCV not detected; no evidence of HCV infection”

+ ve
Report as:
“HCV antibody (or HCV antibody/antigen) DETECTED; ? maternal antibody please repeat investigation in 6 months to confirm”

Paediatric advice based upon National Guidance: Davison et al., Arch.Dis. Child 2006; 91:781-785
Diagnosis of Hepatitis C
Screening of babies/children over 12 months born to HCV infected mothers

Paediatrics
Child of 18 months or older

HCV antibody test

- ve
no further action
Report as: "HCV antibody not detected"

+ ve
confirmatory HCV antibody test

- ve
HCV PCR
Report as: "HCV RNA not detected. Consistent with HCV infection at some time. Suggest monitor liver enzymes over 6 months and repeat investigation in 6 months to confirm virus clearance"

+ ve
refer for assessment
Report as: "Consistent with active hepatitis C virus infection. Needs referral for consideration of treatment as outlined in local care pathway"

OR
HCV antibody test & antigen combination test

- ve
+ ve

Child guidance based upon: Corristine et al., “Guidelines for the testing of looked after children who are at risk of a blood-borne infection. A joint Children’s Services and Health Document. Greater Manchester 2008."
Diagnosis of Hepatitis C
Screening for hepatitis C infection in renal dialysis patients

See also: “Good practice guidelines for renal dialysis/transplantation units: prevention and control of blood-borne virus infection” (Department of Health 2002) and the renal association guidelines: http://www.renal.org/pages/media/download_gallery/BBVinfectionFINAL14July09.pdf

Patients who are HCV infected may have fluctuating levels of HCV antibody; there is evidence that those who are chronically infected are better monitored by application of HCV antigen or HCV combined antigen antibody tests.
Treatment of Hepatitis C
Referral to treatment

Initial assessment at treatment centre

Patients referral - only those shown to be HCV Ab +ve and HCV RNA +ve

Consider Liver Biopsy
Full Haematological Profile
Hepatitis C quantitative PCR
Full Biochemical Profile

Hepatitis C genotyping

ASSESS SUITABILITY FOR TREATMENT

Two forms of treatment are envisaged, treatment within the community for non-cirrhotic and non-co-infected individuals, and treatment of more complex cases within tertiary referral centres. In either case ONLY patients who are known to be hepatitis C RNA positive should be referred for treatment.

For treatment centre testing hepatitis C RNA should be quantified. HCV RNA is measured at intervals through the treatment pathway to allow treatment decisions and to monitor the outcome of treatment.

Quantitative PCR and HCV genotyping are repeated at the treatment centre to confirm the results of testing in the referring centre and to identify those who have spontaneously cleared HCV RNA between the time of diagnosis and their arrival at the treatment centre.

Quantitative PCR has a limit of detection of 30 IU/ml. Samples containing 30 IU/ml or more are reported as HCV RNA detected   HCV RNA DETECTED (x iu/ml: log iu/ml = y) [where x and y are the actual values determined].
Samples containing no detectable HCV RNA are reported as: HCV RNA NOT detected (<30 iu/ml: log iu/ml = <1.48)

The HCV RNA test requires a minimum volume of 1.5ml serum or plasma. If this volume is not available to test a 1/10 dilution of the sample is made in HCV RNA negative plasma before the test is performed. This reduces the test sensitivity slightly. Positive samples will be reported after the quantity of HCV RNA has been corrected for the dilution factor negative samples will be reported as: HCV RNA NOT detected (<300 iu/ml: log iu/ml = <2.48)

Assessment for suitability for treatment may include initial referral for psychological assessment, help with drink addiction or substance misuse addiction.
Treatment of Hepatitis C
Genotype 1/4 hepatitis C without HIV co-infection

- **Genotype 1 or 4**
  - **Viral load <600,000 (log 5.8) IU/ml AND no, or minimal cirrhosis**
    - 24 - 72 weeks of therapy (depending upon response to therapy) as outlined in the local treatment guidelines
  - **Viral load >600,000 (log 5.8) IU/ml AND/or cirrhosis/high fibrosis**
    - Up to 48 weeks of therapy as outlined in the local treatment guidelines
Treatment of Hepatitis C
Genotype 2/3 hepatitis C without HIV co-infection

Genotype 2 or 3

- 24 weeks of therapy as outlined in the local treatment guidelines
- If age > 40 years RNA < 800,000 (log 5.8) IU/ml and only early fibrosis

12 - 24 weeks of therapy as outlined in the local treatment guidelines
For further information please contact
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