Section 3: Testing and Diagnosis of Hepatitis C

Dr. Jules Alla Kouadio (Médecins du Monde)
Training “Hepatitis C and HR for PWUD”,
20th-24th Sept. 2016, Nairobi, Kenya
Learning objective of the session
introducing the participants to the main tests used
to identify exposure to hepatitis C, whether a
person is actively infected and to assess and
monitor liver health
Learning objectives:

1. Recognise the benefits of hepatitis C
2. Discuss antibody testing and RNA testing and explain results
3. Identify the tests used for understanding liver disease progression (biopsy/Fibroscan)
Outline of the presentation

1. Screening of Hepatitis C
2. Confirmation of Hepatitis C
3. Assess the degree of liver fibrosis and cirrhosis
4. Prioritized for treatment
Anti-HCV antibody screening
Screen for other bloodborne viruses

**SCREENING**

RNA test positive

- Harm reduction
  - Address alcohol use
  - Consider OST
  - Vaccinate for HBV
  - Provide sterile injecting equipment
  - Peer intervention

RNA test negative

- Harm reduction
  - Address alcohol use
  - Consider OST
  - Vaccinate for HBV
  - Provide sterile injecting equipment
  - Peer intervention
  - Consider retesting (RNA)

**CARE**

- Stage disease
  - Clinical examination: exclude decompensation for interferon-containing and
  - omibitasvir/paritaprevir/daclatasvir
  - regimens
  - APRI, HCV-4 or TE

**TREATMENT**

- Assess for treatment
  - Consider comorbidities, depression, pregnancy and potential drug–drug interactions
  - Genotype virus

- Select regimens

- Monitor for efficacy and toxicity

APRI: aminotransferase/platelet ratio index; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; OST: opioid substitution therapy; TE: transient elastography

Plan

1. Screening of Hepatitis C
2. Confirmation of Hepatitis C
3. Assess the degree of liver fibrosis and cirrhosis
4. Prioritized for treatment
1. What is an antibody?
2. What does it mean if someone has positive HCV antibody?
HCV natural history
1. Screening of Hep C = antibodies

» HCV antibody test (screening test)

» Anti-HCV usually become detectable between **8 and 12 weeks** after infection and 90% of patients have HCV antibody after 12 weeks.

» In Kenya, MdM used **SD Bioline** and is about to use OraQuick, both are lateral flow immunoassay.
Interpretation of screening test results

» The results are given as reactive and non-reactive.

» Negative result indicates that the person is not infected with Hep C virus.

» But there is risk behaviors, need to confirm again after 12 weeks.

» Positive result indicates that the patients had infected with Hep C virus once in his lifetime. It does not indicate that the patient have Chronic Hepatitis.

» Patients who have viral clearance remain positive for HCV antibody.

» It is important to tell the patient that HCV Ab test is a screening test and once it is positive, the patients needs to confirm with HCV RNA PCR test.
Interpretation of screening test results (1/3)

- The results are given as reactive and non-reactive.
- Negative result indicates that the person is not infected with Hep C virus.
- But there is risk behaviors, need to confirm again after 12 weeks (window period)
- There is a risk of false negative result for HIV+ people
Interpretation of screening test results (2/3)

» Positive result indicates that the patients **had infected with Hep C virus once in his lifetime**. It does not indicate that the patient have Chronic Hepatitis.

» Patients who have viral clearance remain positive for HCV antibody.

» It is important to tell the patient that HCV Ab test is a screening test and once it is positive, the patients needs to confirm with HCV RNA PCR test.
Interpretation of screening test results (3/3)

- Invalid = you must do the test again.
- If 2 rapid tests are invalid you need to perform a viral load test
If someone is anti-HCV positive

» What are you going to tell your patient?

» Is he/she at risk of transmitting the virus?
Plan

1. Screening of Hepatitis C
2. Confirmation of Hepatitis C
3. Assess the degree of liver fibrosis and cirrhosis
4. Prioritized for treatment
Existing recommendation from 2014

It is suggested that nucleic acid testing for the detection of HCV RNA be performed directly following a positive HCV serological test to establish the diagnosis of chronic HCV infection, in addition to nucleic acid testing for HCV RNA as part of the assessment for starting treatment for HCV infection.

*Conditional recommendation, very low quality of evidence*
2. Confirmation of Hep C = viral load

» **HCV RNA PCR** (viral load testing)
  
  – HCV RNA is detected within 1-2 week after initial infection.
  
  – Confirmation test for active HCV infection. Also use for treatment monitoring.
  
  – Qualitative testing: virus there, yes or no?
  
  – Quantitative testing: how much virus is there?
Serologic pattern of acute HCV infection with progression of chronic infection

= Viral load

= antibodies

Figure provided by the Centers for Disease Control and Prevention.
LABORATORY REPORT

RESULT

HCV Viral Load

HCV RNA: NOT DETECTED

Below Detection Limit

This report is generated by Rotor-Gene Real-Time Analysis using assay* HCV RG RT-PCR KIT.

Analytical sensitivity of assay: HCV RG RT-PCR KIT: 33.5 IU/ml

Linear Dynamic Range of assay: HCV RG RT-PCR KIT: 65 IU/ml - 10^6 IU/ml

* assay HCV RG RT-PCR KIT reports the result only in IU/ml and it does not provide conversion from IU/ml to copies/ml. For estimation of viral concentration in copies/ml, the conversion of (A x 10^n) x 4000, n being the number of cycles recommended by WHO paper titled "WHO Consultation on International Standards for In-Vitro Clinical Diagnostic Procedures on Nucleic Acid Amplification Techniques (NAT)" can be considered.

Run Date: 4th May, 2014

Prof. N. Win
M.B.B.S., M.Med.Sc. (Pathology)
MD (Molecular Pathology)
## Laboratory Report

**Patients Name:**

**Age/Sex:**

**Requested By:** Dr. U. Hly Win

**Refereed Center:** Sein Thetwar Medical Lab

**Laboratory Report**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Viral Load</td>
<td>HCV RNA DETECTED</td>
</tr>
<tr>
<td></td>
<td>1.623 x 10^3 IU/ml</td>
</tr>
</tbody>
</table>

*Note: HCV RNA levels are reported in IU/ml. For comparisons of viral load, IU/ml is the denominator. For conversion of viral load from IU/ml to copies/ml, the conversion of (2 IU/ml x 4 copies/IC) is applied. The recommended WHO Consultation on International Standards for In-Vitro Clinical Diagnostic Procedures based on Nucleic Acid Amplification Techniques (IAAT) can be considered.*

**Prof. No Win**

M.B.B.S., M.Med.Sc (Pathology)
Ph.D. (Molecular Pathology)

Room-3, S Y Building, 20 St., Between 77-78 St., Chanmyehtalan Tlp., Mandalay
Phone: 02 72985, 09 5101423
Plan

1. Screening of Hepatitis C
2. Confirmation of Hepatitis C
3. **Assess the degree of liver fibrosis and cirrhosis**
4. Prioritized for treatment
Existing recommendation from 2014

In resource-limited settings, it is suggested that aminotransferase/platelet ratio index (APRI) or FIB-4 be used for the assessment of hepatic fibrosis rather than other non-invasive tests that require more resources such as elastography or FibroTest.

Conditional recommendation, low quality of evidence

Note: This recommendation was formulated assuming that liver biopsy was not a feasible option. FibroScan®, which is more accurate than APRI and FIB-4, may be preferable in settings where the equipment is available and the cost of the test is not a barrier to testing.
3. Assessing level of fibrosis

» **Blood biochemistry:**
  - Aminotransferase/platelets ratio index (APRI)
  - FIB-4

» **Imaging techniques:**
  - Fibroscan (Transient elastography)
  - Ultrasound

» Liver biopsy (previously gold standard for accessing fibrosis; but invasive and risk of complications like bleeding)
<table>
<thead>
<tr>
<th>Test</th>
<th>Components</th>
<th>Requirements</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI</td>
<td>AST, platelets</td>
<td>Simple serum and haematology tests</td>
<td>+</td>
</tr>
<tr>
<td>FIB-4</td>
<td>Age, AST, ALT, platelets</td>
<td>Simple serum and haematology tests</td>
<td>+</td>
</tr>
<tr>
<td>FibroTest</td>
<td>gGT, haptoglobin, bilirubin, A1 apolipoprotein, α2-macroglobulin</td>
<td>Specialized tests. Testing at designated laboratories</td>
<td>++</td>
</tr>
<tr>
<td>FibroScan®</td>
<td>Transient elastography</td>
<td>Dedicated equipment</td>
<td>+++</td>
</tr>
</tbody>
</table>

ALT: alanine aminotransferase; APRI: aminotransferase/platelet ratio index; AST: aspartate aminotransferase; gGT: gamma glutamyl transpeptidase

Online score calculators are available:
http://gihep.com/calculators/hepatology/fibrosis-4-score/
http://www.hepatitis.uw.edu/page/clinical-calculators/apri
Imaging Technique - Fibroscan

- Fibroscan (transient elastography) is measuring mass liver tissue, 1cm in diameter and 5cm in length.
- Vibration towards the liver tissue by ultrasound probe.
- It follows by pulse echo, and velocities are measured.
- Fibrosis is usually indicated with METAVIR Fibrosis score.
Fibroscan (transient elastography)

www.echosens.com
Rockey, *Gastroenterology*, 2008
**Fibroscan exam**

3/29/2016 5:29:08 AM

<table>
<thead>
<tr>
<th>Exam type</th>
<th>Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operator</td>
<td></td>
</tr>
<tr>
<td>Referring Physician</td>
<td></td>
</tr>
<tr>
<td>Median stiffness</td>
<td>4.0 Kpa</td>
</tr>
<tr>
<td>IQR</td>
<td>0.5 Kpa</td>
</tr>
<tr>
<td>IQR/med.</td>
<td>13%</td>
</tr>
<tr>
<td>Valid measures</td>
<td>10</td>
</tr>
<tr>
<td>Success rate</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Legal notice**

FibroScan is a medical device designed for use as a diagnostic aid. Measurements should be performed by a certified operator. Results should be interpreted by a specialist in liver medicine according to the clinical context, taking into account the number of valid measurements, their dispersion (IQR) and the success rate.
**SCORING CARD**

**CORRELATION BETWEEN LIVER STIFFNESS (kPa) & FIBROSIS STAGE**

- **Hepatitis B***
- **HCV-HIV co-infection***
- **Hepatitis C recurrence after liver transplantation***
- **Hepatitis C***
- **Chronic cholestatic diseases***
- **Alcohol***
- **NAFLD***

| Liver Disease | 0 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 75 |
|---------------|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Liver Stiffness (kPa) |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

* F0
* F0-F1
* F1
* F1-F2
* F2
* F2-F3
* F3
* F3-F4
* F4
Metavir Fibrosis score

Ziol Transient Elastography Breakpoints

2.5  8.8  9.6  14.6  75kPa

Metavir  F0-F1  F2  F3  F4
Absent or mild fibrosis  Significant fibrosis  Severe fibrosis  Cirrhosis

<table>
<thead>
<tr>
<th>METAVIR stage</th>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>No fibrosis</td>
<td>Portal fibrosis without septa</td>
<td>Portal fibrosis with septa</td>
<td>Numerous septa without cirrhosis</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>
What will it change in you counselling with the patient?

- To know that the Fib-4, APRI of Fibroscan show an F3 stage?
- Or an F0-F1 stage?
Plan

1. Screening of Hep C
2. Confirmation of Hep C
3. Assess the degree of liver fibrosis and cirrhosis
   - Specific evaluation for cirrhosis
4. Prioritized for treatment
**Plan**

1. Screening of Hep C
2. Confirmation of Hep C
3. Assess the degree of liver fibrosis and cirrhosis
   - Specific evaluation for cirrhosis
4. Prioritized for treatment
prioritize
GUIDELINES FOR THE SCREENING, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS C INFECTION

UPDATED VERSION
APRIL 2016
GUIDELINES
Exercise 1 (30 mins)

Divide participants into groups of 3 to 5 and ask them to complete the table below (you can draw the table on flipcharts)

<table>
<thead>
<tr>
<th>Test outcome</th>
<th>Interpretation</th>
<th>Further Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV antibody -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV antibody +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV antibody +, HCV RNA +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV antibody +, HCV RNA -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test outcome</td>
<td>Interpretation</td>
<td>Further Action</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>HCV antibody -</td>
<td>No HCV antibody detected</td>
<td>If the person has no risk behavior, no further action required. If the person has risk behaviors, need to be tested again after 12 weeks because of window period.</td>
</tr>
<tr>
<td>HCV antibody +</td>
<td>The person has been infected with HCV infection in his lifetime/presumptive HCV infection</td>
<td>Need to test HCV RNA/viral load for the confirmation.</td>
</tr>
<tr>
<td>HCV antibody +, HCV RNA +</td>
<td>Current HCV infection</td>
<td>Need to do liver fibrosis assessment.</td>
</tr>
<tr>
<td>HCV antibody +, HCV RNA -</td>
<td>No current HCV infection: spontaneous cure of treatment successful</td>
<td>No further action required. This person is at risk of reinfection</td>
</tr>
</tbody>
</table>
Exercise 2 (30 mins)

Divide participants into groups of 3 to 5 and ask them to complete the table below (you can draw the table on flipcharts)

<table>
<thead>
<tr>
<th>Test outcome</th>
<th>Interpretation</th>
<th>Further Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI score = &lt;F2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APRI score = F4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibroscan = F0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibroscan = F3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Solution for exercise 2

<table>
<thead>
<tr>
<th>Test outcome</th>
<th>Interpretation</th>
<th>Further Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI score = &lt;F2</td>
<td>no significant fibrosis = Liver not too damaged</td>
<td>No urgent need of treatment Look for factor of progression Reassure the patient Follow up of fibrosis</td>
</tr>
<tr>
<td>APRI score = F4</td>
<td>cirrhosis = Liver damaged</td>
<td>Urgent need of treatment Look for factor of progression Refer to doctor for cirrhosis management</td>
</tr>
<tr>
<td>Fibroscan = F0</td>
<td>No fibrosis</td>
<td>No urgent need of treatment Look for factor of progression Reassure the patient Follow up of fibrosis</td>
</tr>
<tr>
<td>Fibroscan = F3</td>
<td>Significant fibrosis (close to cirrhosis)</td>
<td>Urgent need of treatment Look for factor of progression Follow up of fibrosis, Consider annual fibroscan</td>
</tr>
</tbody>
</table>
This presentation was produced with the financial support of the French development agency (AFD – Agence Française de développement). The ideas and opinions it contains are those of Médecins du Monde and do not necessarily represent those of AFD.