Module 1

Introduction of hepatitis
Training Objectives

At the end of the module, trainees will be able to:

- Demonstrate improved knowledge of the global epidemiology of the viral hepatitis
- Understand and describe the characteristics of each hepatitis virus
- Describe the difference between acute hepatitis and chronic hepatitis
- Describe the sequela of chronic hepatitis
What is Hepatitis?

- The liver is located in the upper right area of the abdomen below the diagram.

What is Hepatitis?

- Hepatitis is inflammation of liver.
- The condition can be self-limiting or if chronic, can progress to fibrosis, cirrhosis, or liver cancer.
- The cause of hepatitis
  - Hepatitis viruses (A, B, C, D, E)
  - Other infections
  - Toxic substance (e.g. alcohol)
  - Autoimmune disease
1.45 million deaths from viral hepatitis per year, (>>the mortality of HIV)

Regional distribution of viral hepatitis deaths

MORTALITY RATE (PER 100,000 PY)
- <10
- 10 - 14.9
- 15 - 22.49
- 22.5 - 33.49
- 33.5+

PROPORTION ATTRIBUTABLE TO EACH VIRUS
- The area of each pie is proportional to the number of hepatitis-attributable deaths in that region:
- each wedge represents the proportion of those deaths attributable to a given virus

Source: Stanaway and Cooke (personal communication)
Mortality from viral hepatitis in the Western Pacific Region in 2013

- Cirrhosis due to hepatitis: 150,009 (27%)
- Acute hepatitis E: 7,375 (21%)
- Acute hepatitis A: 1,482 (4%)
- Acute hepatitis C: 813 (2%)
- Acute hepatitis B: 25,222 (73%)
- Liver cancer due to hepatitis: 382,879 (67%)

Regional Action Plan for Viral hepatitis in the Western Pacific 2016-2020: WPRO
WHO action on viral hepatitis

- “Global Health Sector Strategy on Viral Hepatitis, 2016-2021”.

This strategy has a vision of eliminating viral hepatitis as a public health problem and this is encapsulated in the global targets of reducing new viral hepatitis infections by 90% and reducing deaths due to viral hepatitis by 65% by 2030.

- WHO also organizes World Hepatitis Day on 28 July every year to increase awareness and understanding of viral hepatitis.
Regional action on viral hepatitis to date

The WHO Regional committee for the Western Pacific set the prevalence targets for chronic hepatitis B infection rates among 5-years-old children to:

- Less than 2% by 2012
- Less than 1% by 2017

The Region has largely reached 2017 goal
Region vaccination coverage and number of chronic infections by year of birth
The Regional Action Plan for Viral Hepatitis in the Western Pacific
2016-2020

- Provide an approach specific to viral hepatitis
- Reach beyond immunization
- Build awareness and knowledge among stakeholders
- Strengthen public policy
- Generate data to better understand hepatitis epidemics
- Enhance prevention strategies
- Improve access to affordable screening, diagnosis, and treatment
Main hepatitis viruses

- Hepatitis A virus (HAV)
- Hepatitis E virus (HEV)
- Hepatitis B virus (HBV)
- Hepatitis D virus (HDV)

Chronic infection
Liver cirrhosis
Liver cancer

Hepatitis C virus (HCV)
# Main hepatitis viruses

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute hepatitis</strong></td>
<td>Case fatality increases with age</td>
<td>Case fatality increases with age</td>
<td>Uncommon</td>
<td>Superinfection in HBV may lead to fulminant disease</td>
<td>Higher case fatality in pregnant women</td>
</tr>
<tr>
<td><strong>Chronic infection</strong></td>
<td>No</td>
<td>5% of adults 90% of children</td>
<td>55-85%</td>
<td>Complicates chronic hepatitis B</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Hepatocellular carcinoma</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Route of transmission</strong></td>
<td>Person-to person</td>
<td>Perinatal Bloodborne sexual</td>
<td>Bloodborne Perinatal Sexual</td>
<td>Bloodborne</td>
<td>Waterborne Foodborne</td>
</tr>
<tr>
<td><strong>vaccine</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>HBV vaccine</td>
<td>No</td>
</tr>
<tr>
<td><strong>Treatment options</strong></td>
<td>None</td>
<td>Available</td>
<td>Available</td>
<td>Modified treatment of HBV</td>
<td>None</td>
</tr>
</tbody>
</table>
Hepatitis B

- 240 million people around the world have been infected with HBV.
- 680,000 die every year due to hepatitis B (approximately half of the all hepatitis related deaths)
Hepatitis C

- 80 million people around the world are infected with HCV (viremia)
- 700,000 die every year due to hepatitis C (approximately half of the all hepatitis related deaths)

Reported HCV prevalence –
Number of viraemic HCV infections – all ages.

Acute hepatitis

- No symptoms
- or
- Jaundice
- General fatigue
- Abdominal pain...

Laparoscopic finding
A large reddish liver

Cure /Liver failure
Chronic hepatitis

Liver inflammation persists over 6 months

Liver cirrhosis, Liver cancer (HBV, HCV)

The liver surface becomes uneven

Liver cirrhosis

The liver surface becomes nodular

Liver cancer
Liver cirrhosis is an advanced stage of liver disease

- Chronic hepatitis
- Liver Cirrhosis (compensated)
- Liver Cirrhosis (decompensated)

- Ascites, Variceal hemorrhage
- Hepatic encephalopathy, Jaundice...

- Esophageal varices
- Normal esophagus
Hepatocellular carcinoma

- Hepatocellular carcinoma (HCC) is the histological type of liver cancer that accounts for the large majority of primary liver cancer.
- HBV and HCV are the major causes of HCC
Assessing the liver disease severity

- Platelets ↓
- AST/ALT ↑
- Albumin ↓
- Bilirubin ↑
- Prothrombin time ↑

Developing of cirrhosis
Portal hypertension

Ultrasonography
AFP↑

Hepatocellular carcinoma

Endoscopy
Varices
Assessing the liver disease severity

Child-Turcotte-Pugh score (Child-Pugh score)

<table>
<thead>
<tr>
<th>Points</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Minimal (grade 1 or 2)</td>
<td>Advanced (grade 3 or 4)</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Controlled</td>
<td>Refractory</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)(mg/dL)</td>
<td>&lt;34 (&lt;2)</td>
<td>34-51 (2-3)</td>
<td>&gt;51 (&gt;3)</td>
</tr>
<tr>
<td>Albumin(g/dL)</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Prothrombin time (seconds) or PT-INR</td>
<td>&lt;4 or &lt;1.7</td>
<td>4-6 or 1.7-2.3</td>
<td>&gt;6 or &gt;2.3</td>
</tr>
</tbody>
</table>

PT-INR; prothrombin time international normalized ratio
Child-Pugh Class A: 5-6 points
Child-Pugh Class B: 7-9 points
Child-Pugh Class C: 10-15 points
Case study
A 65 year-old male with liver cirrhosis.
Clinical examination and laboratory data are as follows;
Total bilirubin  32μmol/L
Albumin       3.1 g/dL
PT-INR        1.6
Mild ascites, No encephalopathy

Q. What is the Child-Pugh Class?
Assessing the degree of liver fibrosis

Liver biopsy

**METAVIR liver biopsy scoring system**

<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>

No fibrosis (Acute hepatitis)  
Chronic hepatitis  
Liver cirrhosis
Assessing the degree of liver fibrosis

Non-invasive tests

<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 hematology tests</td>
<td>+</td>
</tr>
<tr>
<td>FIB-4</td>
<td>Age, AST, ALT, Platelets</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>FibroTest</td>
<td>gGT, haptoglobin, bilirubin, A1apoprotein, α2-macroglobulin</td>
<td>Specialized test. Testing at designed laboratories</td>
<td>++</td>
</tr>
<tr>
<td>Fibroscan®</td>
<td>Transient elastography</td>
<td>Dedicated equipment</td>
<td>+++</td>
</tr>
</tbody>
</table>

APRI aspartate aminotransferase-to-platelet ratio index
FIB-4 fibrosis-4 score
ALT alanine aminotransferase, AST aspartate aminotransferase

Operation of transient elastography (fibroscan®)
Assessing the degree of liver fibrosis

<table>
<thead>
<tr>
<th>Fibrosis stages assessed</th>
<th>Cut off values for the detection of fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cirrhosis (META VIR F4)</td>
</tr>
<tr>
<td></td>
<td>Significant fibrosis (META VIR $\geq$ F2)</td>
</tr>
<tr>
<td>APRI</td>
<td>High cut-off 2.0</td>
</tr>
<tr>
<td>$\geq$ F2, F4</td>
<td>High cut-off 1.5</td>
</tr>
<tr>
<td>FIB-4</td>
<td>High cut-off 3.25</td>
</tr>
<tr>
<td>$\geq$ F3</td>
<td></td>
</tr>
<tr>
<td>FibroTest</td>
<td>0.32-0.48</td>
</tr>
<tr>
<td>$\geq$ F2, F3, F4</td>
<td>0.58-0.75</td>
</tr>
<tr>
<td>Fibroscan®</td>
<td>&gt;11-14kPa</td>
</tr>
<tr>
<td>$\geq$ F2, F3, F4</td>
<td>&gt;7-8.5kPa</td>
</tr>
</tbody>
</table>

APRI aspartate aminotransferase-to-platelet ratio index
FIB-4 fibrosis-4 score
APRI and FIB-4 formulas

- **APRI** = \[
\frac{(\text{AST(IU/L)})}{\text{AST}_\text{ULN}(\text{IU/L})} \times 100 \] / platelet count (10^9/L)

  For APRI, ULN signifies the upper limit of normal for AST in the laboratory where these investigations were undertaken.

- **FIB-4** = \[\text{age(yr)} \times \frac{\text{AST(IU/L)}}{\text{platelet count}(10^9/L)} \times \left[\text{ALT}(\text{IU/L})^{1/2}\right]\]

Module review

- What is hepatitis?
- How common is viral hepatitis in the world and in your country?
- What hepatitis virus cause acute hepatitis?
- What hepatitis virus cause chronic hepatitis?
- What is the sequela of chronic hepatitis?