Practical Approach to Hepatitis B Management

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Outline

Background:

– burden of disease, transmission and natural history of CHB, a dynamic disease.

Testing:

– screening, diagnosis and interpretations of results

Assessment and treatment:

– WHO Guidelines 2015
Hepatitis B is a serious global problem

• 2 billion people worldwide have been infected with HBV and ~350 million chronic carriers

• Leading cause of cirrhosis and HCC

• 2\textsuperscript{nd} only to tobacco in causing the most cancer deaths

• HBV is 50-100 x more infectious than HIV

• Vaccine preventable (Malaysia-1989)
HBV transmission

Blood and bodily fluids exposure through a break in skin or mucus membrane.

Also found in semen, saliva, vaginal mucus, and tears but at levels 1000 x lower cf serum

Not found in urine, sweat, or stool.

The most common mode of transmission in Asia Pacific is perinatal leading to high rates of chronicity.
Natural history of CHB infection acquired perinatally and during infancy

Liaw and Chu. Lancet 2009
CHB is a dynamic disease

After spontaneous HBeAg seroconversion, 67% to 80% of carriers remain in inactive carrier phase.

4% to 20% of inactive carriers have reversion back to HBeAg positive CHB.

10% to 20% have reactivation after yrs of quiescence disease.

HBeAg-negative CHB

CHB is a dynamic disease

After spontaneous HBeAg seroconversion, 67% to 80% of carriers remain in inactive carrier phase

4% to 20% of inactive carriers have reversion back to HBeAg positive CHB

10% to 20% have reactivation after yrs of quiescence disease

(HBeAg-negative CHB)

Therefore monitoring and serial testing is necessary during the “inactive carrier state”

Knowing the natural history of CHB helps
Screening-who to test for hepatitis B?

- WHO 2015:
  - Household and sexual contacts of persons with CHB,
  - HIV-infected persons,
  - Persons who inject drugs (PWID),
  - Men who have sex with men, sex workers,
  - Other groups: indigenous peoples, persons who are incarcerated, and persons of transgender.

- All candidates for chemotherapy and immunosuppressive therapy
  (EASL 2012- HBsAg and anti-HBc, APASL 2012-HBsAg)
Screening - which tests to order?

• HBsAg - first step
• Chronic hepatitis B is defined as HBsAg positive > 6 months
Assessments - further investigations?

• Assess for other serological markers and viral replication/load:
  o HBeAg, antiHBe
  o HBVDNA (especially if HBeAg negative)

• Assess the severity of liver disease (fibrosis, cirrhosis; compensated vs decompensated):
  o LFT/INR/PLT/AFP/US/OGD-evidence of portal hypertension/HCC
• Liver biopsy/NIT (stage of fibrosis (F0-F3) :
  o APRI/FIB-4, Fibrotest, Transient elastography

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. WHO Mar 2015
# Interpretations of serological markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Acute HBV</th>
<th>Acute HBV Recovery</th>
<th>Chronic HBV Disease</th>
<th>Inactive Carrier State</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>(may clear fast)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBe</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
## Interpretations of serological markers

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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HBeAg Positive</td>
<td>HBeAg Negative</td>
</tr>
<tr>
<td>HBsAg</td>
<td>✓</td>
<td>(may clear fast)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HBeAg</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Anti-HBe</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Anti-HBc IgM</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Assessments - further investigations?

- Assess the severity of liver disease:
  (fibrosis vs cirrhosis; compensated vs decompensated)
  - LFT/INR/PLT/AFP/US
  - If cirrhotic: OGD-evidence of portal hypertension/HCC surveilance

- Liver biopsy/non invasive tests (NIT) for stage of fibrosis:
  - APRI/FIB-4, Fibrotest, Transient elastography

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. WHO Mar 2015
NIT for assessment of liver fibrosis

APRI = \* \frac{(AST/ULN) \times 100)}{\text{platelet count} \, (10^9/L)}

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

Meta-analysis: APRI and FIB-4 identify fibrosis in CHB with moderate sensitivity & accuracy.

Online calculators: APRI at http://www.hepatitisc.uw.edu/page/clinical-calculators/apri
FIB-4 at http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

<p>| Table 3. Meta-analysis results of LSM cutoff values for staging liver fibrosis. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Weighted Mean LSM value (kPa)</th>
<th>Range (kPa)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F = 2</td>
<td>1,625</td>
<td>7.9</td>
<td>6.1-11.8</td>
<td>74.3</td>
</tr>
<tr>
<td>F = 3</td>
<td>960</td>
<td>8.8</td>
<td>8.1-9.7</td>
<td>74.0</td>
</tr>
<tr>
<td>F = 4</td>
<td>2,051</td>
<td>11.7</td>
<td>7.3-17.5</td>
<td>84.6</td>
</tr>
</tbody>
</table>

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. WHO Mar 2015; Guangqin Xiao et al Hepatology 2015; Chon YE et al. PLOS One 7(9) e44930
### NIT cut-off values for cirrhosis or significant fibrosis

APRI = \* \((\text{AST/ULN}) \times 100\) / \(\text{platelet count} \times 10^9/\text{L}\)

FIB-4 = \((\text{age} \times \text{AST} \times \text{ULN}) \times (\text{platelet count} \times 10^9/\text{L} \times [\text{ALT} \times \text{ULN}]^{1/2})\)

<table>
<thead>
<tr>
<th></th>
<th>APRI (low cut-off)</th>
<th>APRI (high cut-off)</th>
<th>FIB-4</th>
<th>Fibrotest</th>
<th>Transient elastography (Fibroscan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>1.0</td>
<td>2.0</td>
<td>--</td>
<td>0.32–0.48</td>
<td>&gt;11–14 kPa</td>
</tr>
<tr>
<td>(METAVIR F4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant fibrosis</td>
<td>0.5</td>
<td>1.5</td>
<td>1.45</td>
<td>0.58–0.75</td>
<td>&gt;7–8.5 kPa</td>
</tr>
<tr>
<td>(METAVIR ≥F2)</td>
<td></td>
<td></td>
<td>(low)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Other important managements in CHB pts

- **Assess for co-morbidities:**
  Co-infection (HIV, HCV), impaired GT, dyslipidemia, NAFLD, ALD, drugs/toxin induced injury

- **Preventive measures:**
  Notifications, HBsAg screening + HBV vaccination of family members and sexual contacts.

- **Counselling:**
  Educate pt on the risk of transmission to others and preventive measures, risk of DILI, HAV vaccination, ethanol/smoking, lifestyle, diet, physical activity.

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. WHO Mar 2015
Monitoring for hepatocellular carcinoma

Methods: US and AFP testing every 6 months:

Who?

- cirrhosis, regardless of age or other risk factors
- family history of HCC
- > 40 years old (lower age may apply according to regional incidence of HCC), without clinical evidence of cirrhosis (or based on APRI score ≤2), and with HBV DNA level >2000 IU/mL (where HBV DNA testing is available).

Note: AFP > 200 ng/mL = high PPV for HCC in cirrhotics with a mass in the liver. AFP may be normal or near-normal in 40% of patients with HCC.
Who needs treatment?
Who needs treatment?

• As a priority

All CHB with clinical evidence of compensated or decompensated cirrhosis should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels.

*(Strong recommendation, moderate quality of evidence)*

• Treatment is recommended

For adults with CHB who do not have clinical evidence of cirrhosis (or based on APRI score ≤2 in adults), but are aged more than 30 years (in particular), and have persistently abnormal ALT levels and evidence of high-level HBV replication (HBV DNA >20 000 IU/mL), regardless of HBeAg status.

*(Strong recommendation, moderate quality of evidence)*

Note: Persistently normal/abnormal ALT = 3 ALT determinations <ULN made at unspecified intervals over 6–12-mo period or predefined intervals during 12-mo period>
Persistently normal/abnormal ALT = 3 ALT determinations /> ULN made at unspecified intervals over 6–12–mo period or predefined intervals during 12-mo period
HBV Treatment Landscape in 2015

- Interferon alfa-2b (1990)
- Lamivudine (1998)
- Peginterferon alfa-2a (2002)
- Entecavir (2005)
- Adefovir (2006)
- Telbivudine (2008)
- Tenofovir (2008)
# Types of HBV therapy

<table>
<thead>
<tr>
<th>Anti-viral agents</th>
<th>Potency against HBV</th>
<th>Barrier to drug resistance</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferons</td>
<td>Moderate</td>
<td>No resistance</td>
<td>High but finite duration</td>
</tr>
<tr>
<td>Tenofovir (generic)</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Entecavir</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Moderate-High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
</tbody>
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## HBV therapy—recommended by WHO

<table>
<thead>
<tr>
<th>Anti-viral agents</th>
<th>Potency against HBV</th>
<th>Barrier to drug resistance</th>
<th>Cost in Malaysia</th>
</tr>
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<tr>
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<tr>
<td>Adefovir</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
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</table>
Preparing patient to start treatment

Explain and inform patient:

– the indications for treatment
– likely benefits/SE
– treatment targets, most likely need for long term treatment
– need for FU monitoring on and off therapy
– need for adherence (for effectiveness of treatment and also to reduce drug resistance),
– cost implications.
Prolonged AVT improves liver HT and even reverse cirrhosis in CHB

- The goal of treatment for CHB: achieve viral suppression, control liver fibrosis and prevent progression to hepatic decompensation and HCC

Table 1: Rate of the regression of fibrosis in patients with chronic hepatitis B and cirrhosis treated with nucleos(t)ide analogues.

<table>
<thead>
<tr>
<th>Patient N.</th>
<th>HBeAg status</th>
<th>Regression of fibrosis 1</th>
<th>Regression of fibrosis 2</th>
<th>Regression of fibrosis 3</th>
<th>Regression of fibrosis 5 (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>30</td>
<td>+</td>
<td></td>
<td></td>
<td>67%</td>
</tr>
<tr>
<td>Adefovir</td>
<td>16</td>
<td>-</td>
<td>75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>+</td>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90/125</td>
<td>±</td>
<td>49%/12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td>10</td>
<td>±</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>+</td>
<td>96%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10*)</td>
<td>±</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>133</td>
<td>±</td>
<td>68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(96*)</td>
<td>±</td>
<td>74%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>176/250</td>
<td>±</td>
<td>71%/67%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telbivudine</td>
<td>921/446</td>
<td>±</td>
<td>65%/67%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5 years data on Tenofovir

HBeAg-/HBeAg+

Stopping treatment-in the lucky few

• Cirrhosis-do not stop treatment, need lifelong therapy

• In non cirrhotic if :
  – HBeAg loss and seroconversion to antiHBe and persistently normal ALT and persistently undetectable HBVDNA and after at least 1 additional year of consolidation therapy
  – Persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of prior HBeAg status.
  – And the patient can be followed carefully for reactivation

• Relapse is common: monitoring ALT and HBV DNA monthly for the first 3 months then every 3 months during the first year to avoid severe exacerbations
Curing Hepatitis B - the holy grail
by eliminating all replicative forms, incl covalently closed circular DNA

Immune modulation
- Toll-like receptors agonists, Gilead, Roche
- Anti-PD-1 mAb, BMS, Merck
- Vaccine therapy Transgene, Gilead, Roche Innovo, Medimmune, ITS

RNA interference, Arrowhead, Tekmira, Alnylam, GSK

Inhibitors of HBsAg release, Replicor

Polymerase inhibitors
- Nucleoside analogues, e.g. Gilead, BMS
- Non-nucleoside, e.g. LB80380

Entry inhibitors
- Lipopeptides, e.g. Myrcludex-B

Targeting cccDNA

Development stage: preclinical, clinical
CASE DISCUSSION
A 17 years old female presented to your clinic

- She told you her older sister was just found to have CHB when she was screened before entering nursing school.

1) Who should be screened for hepatitis B (HBsAg)?
   a) This patient and her mother
   b) This patient and all her siblings
   c) The household and sexual contacts of this patient’s older sister
A 17 years old female presented to your clinic

- She told you her older sister was just found to have CHB when she was screened before entering nursing school.

1) Who should be screened for hepatitis B (HBsAg)?
   a) This patient and her mother
   b) This patient and all her siblings
   c) The household and sexual contacts of this patient’s older sister
A 17 years old female presented to your clinic

• Test results
  – HBsAg = positive
  – HBeAg = positive
  – HBeAb = negative
  – ALT = 18 IU/L
  - Platelet count = 370,000
  - Fibroscan = 2.8KPa
  - AntiHAV total = negative

2) Which phase of chronic hepatitis B is the patient in?
   a) Immune clearance phase
   b) Inactive carrier phase
   c) Immune tolerant phase
A 17 years old female presented to your clinic

• Test results
  – HBsAg = positive
  – HBeAg = positive
  – HBeAb = negative
  – ALT = 18 IU/L

- Platelet count = 370,000
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Liaw and Chu. Lancet 2009
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  – HBeAb = negative
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2) Which phase of chronic hepatitis B is the patient in?
   a) Immune clearance phase
   b) Inactive carrier phase
   c) Immune tolerant phase

3) How would you manage this patient?
   a) Advise HAV vaccination and treatment for hepatitis B
   b) Advise HAV vaccination and since treatment is not needed, patient can be discharged
   c) Advise HAV vaccination and monitoring with LFT at least 3 times over 6-12 mo
A 17 years old female presented to your clinic

- Test results
  - HBsAg = positive
  - HBeAg = positive
  - HBeAb = negative
  - ALT = 18 IU/L

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   a) Advise HAV vaccination and treatment for hepatitis B
   b) Advise HAV vaccination and since treatment is not needed, patient can be discharged
   **c) Advise HAV vaccination and monitoring with LFT at least 3 times over 6-12 mo**
The patient’s mother 42 yo was also detected to have positive HBsAg

- Test results
  - HBsAg = positive
  - HBeAg = negative
  - HBeAb = positive
  - ALT = 12 IU/L
  - Platelet count = 257,000
  - Fibroscan = 6.1 KPa
  - AntiHAV total = positive
  - HBVDNA = 1,214 iu/ml

1) How would you manage this patient?
   a) Advise treatment for hepatitis B
   b) Advise treatment is not needed and discharge patient.
   c) Advise monitoring with LFT at least 3 times over 6-12 mo, US at baseline and for HCC surveillance and repeat HBVDNA
The patient’s mother 42 yo was also detected to have positive HBsAg

- Test results
  - HBsAg = positive
  - HBeAg = negative
  - HBeAb = positive
  - ALT = 12 IU/L
  - Platelet count = 257,000
  - Fibroscan = 6.1 KPa
  - AntiHAV total = positive
  - HBVDNA = 1,214 iu/ml

1) How would you manage this patient?
   a) Advise treatment for hepatitis B
   b) Advise treatment is not needed and discharge patient.
   c) Advise monitoring with LFT at least 3 times over 6-12 mo, US at baseline and for HCC surveillance and repeat HBVDNA
Patient’s mother 42 yo

• 3 months later: ALT = 98 iu/ml

2) How would you manage this patient now?
   a) Advise treatment for hepatitis B
   b) Advise monitoring with LFT and repeat HBVDNA
   c) Advise a liver biopsy
Patient’s mother 42 yo

• 3 months later: ALT = 98 iu/ml

2) How would you manage this patient now?
   a) Advise treatment for hepatitis B
   b) Advise monitoring with LFT and repeat HBVDNA
   c) Advise a liver biopsy
Patient’s mother 42 yo

- 3 months later: ALT=98 iu/ml
- 4 months later: ALT=20 iu/ml

3) How would you manage this patient?

a) Advise monitoring with LFT and this change in ALT is due to CHB
b) Inform patient that she is an inactive carrier and she does not need treatment
c) Advise to continue follow-up and monitoring with LFT/HBV DNA. Also address any other factors which cause rise in ALTs.
Patient’s mother 42 yo

- 3 months later: ALT=98 iu/ml
- 4 months later: ALT=20 iu/ml

3) How would you manage this patient?
   a) Advise monitoring with LFT and this change in ALT is due to CHB
   b) Inform patient that she is an inactive carrier and she does not need treatment
   
   c) Advise to continue follow-up and monitoring with LFT/HBVDNA. Also address any other factors which cause rise in ALTs.
Persistently normal/abnormal ALT = 3 ALT determinations /> ULN made at unspecified intervals over 6–12–mo period or predefined intervals during 12-mo period
THANK YOU