HBV
Epidemiology & Diagnosis

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HBV is a lifelong, dynamic disease.

Changes over time:
- Risk of end stage liver disease and HCC increases with ongoing inflammation and viremia in adults.
- Fibrosis can be reversible.
- Drugs can decrease fibrosis progression.
- HBV can be controlled but not cured.
- Reactivation can occur even in those who have lost HBsAg.
Hepatitis B Virus Infection Worldwide Disease Burden

- ~2 billion people are infected with HBV worldwide with past infection
- ~250 million persons are estimated suffering this infection
- 15%-25% will die from chronic liver disease (HCC or cirrhosis)
- 30% to 50% of HCC associated with HBV in the absence of cirrhosis
- Second only to tobacco in causing the most cancer deaths
- HBV is 50-100 times more infectious than HIV
Transmission of HBV

HBV is transmitted via contact with blood or body fluids.
Vertical: Infected mother-to-infant

Horizontal:
- Household exposure
- Multiple sexual partners
- Intravenous drug use
- Contaminated needle and due to infected medical devices
Geographic Distribution of Chronic HBV Infection

- Many of the data relating to the global distribution of HBV are over 10-15 years old
- More recent data suggest that this is an over-simplification
- There is an increasing trend towards HBeAg-negative HBV in many areas
- Global distribution of HBV is being affected by population movements from high prevalence areas

<table>
<thead>
<tr>
<th>Chronic infection prevalence</th>
<th>Past infection prevalence</th>
<th>Predominant age at infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 8% – High</td>
<td>40– 90%</td>
<td>Perinatal and early childhood</td>
</tr>
<tr>
<td>2–7% – Intermediate</td>
<td>16– 55%</td>
<td>Early childhood</td>
</tr>
<tr>
<td>&lt; 2% – Low</td>
<td>4– 15%</td>
<td>Adult</td>
</tr>
</tbody>
</table>
Outcome of HBV Infection According to Age at Time of Infection

Chronic infection
Symptomatic acute infection

WHO 2001

National Vaccination of Infants in Iran

• In I.R. Iran mass vaccination of neonates against HBV infection was started from 1993 as a national program in routine neonates care.

• This program is supposed to affect the prevalence rate of HBV infection thorough the country and decrease the rate of infection.

In Iran the mass vaccination program started at 1993 and reached to 94% coverage in 2005 and the reported prevalence of HBV infection in Iran decreased from about 3.5% in 1990s to 2.14% in 2000.
This change is significant but the mass vaccination program is supposed to have more significant decrease on HBV infection prevalence.

Technology developments also provided more sensitive and accurate diagnostic tools that this also may explain the lower decrease trend in HBV infection rates during past decade despite mass vaccination program.
REVIEW

The Changing Epidemiology of Viral Hepatitis B in Iran

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1) Research Center for Gastroenterology and Liver Disease, University of Medical Sciences, Baqiyatallah.
2) Gastroenterohepatology Research Center, University of Medical Sciences, Shiraz, Iran

Abstract

Hepatitis B virus (HBV) prevalence has decreased dramatically in Iranian population during the last decade, and now it is classified as having low endemicity for hepatitis B infection. Improvement of the people’s knowledge about HBV risk factors, national vaccination program since 1993 for all neonates, and vaccination of high risk groups could from chronic HBV infection. Of these, 75% are Asians (1,2). Hepatitis B infection is the 10th leading cause of death worldwide, and results in 500,000 to 1.2 million deaths per year caused by chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). HCC accounts for 320 000 deaths per year (3). The prevalence of HBV infection varies widely, with rates ranging from 0.1% to 20% in different parts of the world (3). Overall, 45% of the world population
HBV Prevalence in Iran

Polled estimated prevalence of HBV infection in the general population of Iran was 2.2%

- Province with Highest Prevalence: Golestan (8.9%)
- Province with Lowest Prevalence: Kermanshah (0.7%)
- Prevalence in Men: 3%
- Prevalence in Women: 1.7%
- Prevalence before 2010: 2.9%
- Prevalence after 2010: 1.3%

HBsAg prevalence, adults (19–49 years), 2005

- <2%
- 2–4%
- 5–7%
- ≥8%
- Not applicable

Decreasing prevalence in some endemic countries, e.g. Taiwan
Possible reasons:
- Improved socioeconomic status
- Vaccination
- Effective treatments

Increasing prevalence in some European countries:
- Migration from high endemic countries
Hepatitis B Virus Diagnosis
The natural history of chronic HBV infection has been schematically divided into Five Phases.
### New nomenclature

<table>
<thead>
<tr>
<th></th>
<th>HBeAg positive</th>
<th>HBeAg negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic HBV infection</td>
<td>High</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Phase 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>High/intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>Phase 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic HBV infection</td>
<td>Low</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Phase 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Phase 5</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolved HBV infection</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

| **HBsAg**          | High           | Low            | Intermediate | Negative |
| **HBeAg**          | Positive       | Negative       | Negative     | Negative |
| **HBV DNA**        | >10^7 IU/mL    | 10^4–10^7 IU/mL | >2,000 IU/mL | <10 IU/mL |
| **ALT**            | Normal         | Elevated       | Elevated†    | Normal   |
| **Liver disease**  | None/minimal   | Moderate/severe | None         | Moderate/severe | None$§$

### Old terminology

<table>
<thead>
<tr>
<th></th>
<th>Immune tolerant</th>
<th>Immune reactive HBeAg positive</th>
<th>Inactive carrier</th>
<th>HBeAg negative * chronic hepatitis</th>
<th>HBsAg negative /anti-HBc positive</th>
</tr>
</thead>
</table>
Phases of chronic HBV infection

HBeAg-positive chronic hepatitis B
HBeAg-positive chronic HBV infection
HBeAg-negative chronic hepatitis B
HBeAg-negative chronic HBV infection

New nomenclature:

2. EASL CPG HBV. J Hepatol 2017;67:370–98
Progression to Chronic Hepatitis B Virus Infection

- IgM anti-HBc
- Total anti-HBc
- HBsAg
- Acute (6 months)
- Chronic (Years)
- HBeAg
- anti-HBe
- Total anti-HBc
- IgM anti-HBc

Titre

Weeks after Exposure

0 4 8 12 16 20 24 28 32 36 52

Years
## Interpretation of Laboratory Tests in Hepatitis B

<table>
<thead>
<tr>
<th>Test</th>
<th>Acute Hepatitis B</th>
<th>Immunity through Infection</th>
<th>Immunity through Vaccination</th>
<th>HBeAg-Pos HBV Infection</th>
<th>HBeAg-Pos Hepatitis B</th>
<th>HBeAg-Neg Hepatitis B</th>
<th>HBeAg-Pos HBV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBsAb</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HBeAg</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HBeAb</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBcAb IgM</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HBcAb total</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>&gt;20,000 IU/mL</td>
<td>&gt;20,000 IU/mL</td>
<td>&gt;20,000 IU/mL</td>
<td>&lt;2,000 IU/mL</td>
</tr>
<tr>
<td>ALT</td>
<td>Elevated</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Notes:**
- Elevated: Above normal range
- Normal: Within normal range
Initial assessment of chronic HBV infection

In addition, all first degree relatives and sexual partners of subjects with chronic HBV infection should be advised to be tested for HBV serological markers (HBsAg, anti-HBs, anti-HBc) and to be vaccinated if they are negative for these markers.
• HBeAg and anti-HBe detection are essential for the determination of the phase of chronic HBV infection.

• Measurement of **HBV DNA serum level** is essential for the diagnosis, establishment of the phase of the infection, the decision to treat and subsequent monitoring of patients.

• HBSAg Level? HBV Genotyping?
Co-morbidities, including alcoholic, autoimmune, metabolic liver disease with steatosis or steato-hepatitis and other causes of chronic liver disease should be systematically excluded including co-infections with hepatitis D virus (HDV), hepatitis C virus (HCV) and HIV.
Liver Function Test:

1. Alanine transaminase (ALT)
2. Aspartate transaminase (AST)
3. Alkaline phosphatase (ALP)
4. Albumin and total protein
5. Bilirubin
6. Gamma-glutamyltransferase (GGT)
7. L-lactate dehydrogenase (LDH)
8. Prothrombin time (PT)
The assessment of the severity of liver disease

1-An abdominal hepatic ultrasound is recommended in all patients.

2-A liver biopsy or a non-invasive test should be performed to determine disease activity in cases where biochemical and HBV markers reveal inconclusive results.
Liver Biopsy:

- Percutaneous liver biopsy.

- Two other types of liver biopsy: Transjugular and Laparoscopic
Liver biopsy

Remains reference method (METAVIR Score: F1-F4)

25 mm long necessary for optimal diagnosis:

Costly, Invasive, Needs trained pathologist,

rare but potentially life threatening complications
Non Invasive Fibrosis scores
Indirect serum Fibrosis Markers

<table>
<thead>
<tr>
<th>Panel</th>
<th>Liver Disease</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT ratio</td>
<td>AST/ALT</td>
<td>53%</td>
<td>100%</td>
<td>100%</td>
<td>81%</td>
</tr>
<tr>
<td>Forns test</td>
<td>Platelets, GGT, Cholesterol</td>
<td>94%</td>
<td>51%</td>
<td>40%</td>
<td>96%</td>
</tr>
<tr>
<td>APRI</td>
<td>AST, Platelets</td>
<td>41%</td>
<td>95%</td>
<td>88%</td>
<td>64%</td>
</tr>
<tr>
<td>Fibrotest</td>
<td>GGT, haptoglobin, bilirubin, apo A, alpha2-macroglobulin</td>
<td>87%</td>
<td>59%</td>
<td>63%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.
Direct serum Fibrosis Markers

**Fibro Meter**: PLT, PT, AST, Hyaluronate, urea, alfa2 macroglobulin, age

crypt algorithm, good performance in F4, not validated in HBV

**Hepascore**: bilirubine, hyluronate, bilirubine, GGT, age, gender

crypt algorithm, good performance in F4, not validated in HBV
Serum biomarkers

- Non specific of the liver
- Limitations: hemolysis, Gilbert, inflammation
- Cost (Fibrotest proprietary)
LIVER STIFFNESS MEASUREMENT
FIBROSCAN

1. Mechanic wave propagates in hepatic tissue
2. Speed propagation measurement by US
3. Stiffness calculation depend on speed kPa
THE EXPLORED VOLUME OF THE LIVER

FNB
Liver tissue of 1 mm Ø X 4 cm

Fibroscan
Liver tissue of 10 mm Ø x 4 cm

X 100
2.5 cm
1 cm Ø
4 cm
Explored volume
# Fibroscan (transient elastography-TE)

<table>
<thead>
<tr>
<th>Pro:</th>
<th>Con:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Widely used, validated</td>
<td>• Dedicated device</td>
</tr>
<tr>
<td>• User friendly</td>
<td>• Intermediate fibrosis not</td>
</tr>
<tr>
<td>• Quality criteria defined</td>
<td>discriminated</td>
</tr>
<tr>
<td>• Good reproducibility</td>
<td>• Not applicable in</td>
</tr>
<tr>
<td></td>
<td>obesity, ascites</td>
</tr>
</tbody>
</table>
Fibroscan (TE), failures

• Failure to obtain any measurement: 3.1%

• Unreliable results: 15.8%

• Risk of overestimation: ALT flares, extra-hepatic cholestasis, congestive heart failure, food/alcohol intake
CIRRHOSIS

Transient elastography:
Negative predictive value = 96%
Positive predictive value = 74%
• TE and serum biomarkers have equivalent performance for detecting significant fibrosis in patients with viral hepatitis

• TE is the most accurate non-invasive method for detecting cirrhosis in patients with viral hepatitis
Thank You
For Your attention