APPROACH TO A PATIENT WITH CHRONIC HEPATITIS B INFECTION

Dr. Mohammad Zahiruddin
Associate Professor
Department of Medicine
Dhaka Medical College
Mr. Alam is a 32 yr old welder, who has been selected for a job in Oman. Unfortunately during his medical screening he turned out to be HBsAg positive.

The ball is now in your court as he presents his case to you and wants to know how to get reed of it.

A dilemma that we physicians face Every day.

Today I will take a journey along with you to discover what we can do for these set of patients.
INTRODUCTION
Introduction

- Chronic Hepatitis B (CHB) infection remains a serious global health challenge.
- Hepatitis B is one of the leading cause of medical unfitness in our country.
- Chronic hepatitis B can lead to liver fibrosis, liver cirrhosis, liver failure and hepatocellular carcinoma (HCC).
HBV Virology

- Partially ds DNA genome, 42nm
- 4 genes – HBsAg, HBcAg, HBV Pol/RT, X protein
- Serologic marker of HBV infection: HBsAg
- Serologic markers of HBV replication: HBeAg, HBV DNA, HBV Polymerase
EPIDEMIOLOGY
Epidemiology

- Over the years de novo HBV infection has decreased.
- Mainly due to effective vaccination.
- CHB effects over 400 million people worldwide.¹
- 75% of them reside in Asia and Western Pacific.²

Epidemiology

- Each year around 1.2 million die of HBV related chronic liver disease.
- CHB is the major cause of HCC, causing 60-80% of the world’s liver cancer.

http://www.who.int/vaccines-surveillance/graphics/htmls/hepbprev.htm
Prevalence of HBV and Incidence of Hepatocellular Carcinoma (HCC)

World prevalence of HBV carriers

HBsAg carriers – prevalence

- <2%
- 2–7%
- >8%
- Poorly documented

Annual incidence of primary HCC

Cases/100,000 population

- 1–3
- 3–10
- 10–150
- Poorly documented

WHO 1999
Epidemiology

- Bangladesh is a country of intermediate prevalence for HBV.¹
- HBV is endemic in Bangladesh.¹
- Community studies in Dhaka have showed the prevalence of CHB to be 5.5 to 5.9%.²
- Other than a few there is a lack of reliable data regarding HBV in Bangladesh.

1.WHO-GAR 2011.
Transmission Of HBV

- Vertical / perinatal transmission.
- Horizontal transmission through minor cuts and breaks in the skin or mucous membranes especially among children with close bodily contact.
- Homosexual or heterosexual sexual contact
- Intravenous drug use
- Transfusion (blood, blood products)
- Organ & tissue transplantation
HIGH RISK GROUPS FOR HBV INFECTION
HIGH RISK GROUPS FOR HBV INFECTION

Persons born In Hyperendemic areas

- Individuals born in high & intermediate prevalent area for HBV
  - Asia: All countries (except Sri Lanka)
  - Africa: All Countries
  - South Pacific Island: All Countries and Territories
  - Middle East: All Countries Except Cyprus
  - Western Europe: Greece, Italy, Malta, Portugal and Spain.
HIGH RISK GROUPS FOR HBV INFECTION

✓ Eastern Europe: All countries except Hungary
✓ The Arctic: Indigenous populations
✓ South America: Argentina, Bolivia, Brazil Ecuador, Guyana, Suriname, Venezuela, and Amazon regions of Colombia, and Peru
✓ Central America: Guatemala and Honduras
✓ Caribbean: Antigua and Barbuda, Dominica, Granada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, and Turks and Caicos.

Other High Risk Groups

- All patients undergoing chemo- or immuno-suppressive therapy
- Indigenous population
- Household contact with someone diagnosed with CHB
- Injecting drug user
- All pregnant women
Other High Risk Groups

- Men who have sex with men
- Infected with HCV or HIV
- Patients undergoing renal dialysis
- Persons with multiple sexual partners or history of sexually transmitted disease

NATURAL HISTORY OF HEPATITIS B
Acute hepatitis B develops 6-12 weeks following exposure to the virus and is marked by serological and biochemical evidence of infection.

HBV related symptoms are rare in the perinatal setting but relatively common in adult-acquired infection.

Mortality from development of acute liver failure occurs in <1% of cases.

Acute HBV: Variable outcomes

- **Complete recovery** with development of anti-HBV immunity may occur.

- **Progression to chronic infection**,  
  - In perinatally exposed (and unvaccinated) infants: 90%  
  - In children age under 5 years: 30%  
  - In adults: < 5%

Risk of CHB Infection Decreases with Age of Acquisition

% Risk of Developing Chronic HBV

Age at Infection

Natural history: chronic HBV

- CHB is defined as persistent detection of HBsAg for >6 months after initial exposure to the virus.
- The natural history of CHB can be categorized into four successive phases of variable duration:
  - Phase I – Immune Tolerance
  - Phase II – Immune Clearance
  - Phase III – Immune Control
  - Phase IV – Immune Escape
Natural history: chronic HBV

Immune Tolerance

- HBs Ag persistent for > 6 months
- ALT persistently normal
- HBV DNA ≥20,000 IU/ml
- Liver Histology normal or mild hepatitis
Natural history: chronic HBV

Immune Clearance

- HBsAg > 6 months
- HBeAg positive
- Seroconversion to Anti HBe may occur
- ALT persistently or intermittently elevated
- HBV DNA ≥20,000 IU/ml
- Liver biopsy moderate to severe hepatitis and cirrhosis.
Natural history: chronic HBV

Immune Control

- HBsAg > 6 months
- HBeAg negative
- Anti HBe positive
- ALT persistently normal.
- HBV DNA <2000 IU/ml
- Liver biopsy normal or mild hepatitis and inactive cirrhosis.
Natural history: chronic HBV

Immune Escape

- HBsAg > 6 months
- HBeAg negative
- Anti HBe positive
- ALT persistently or intermittently elevated.
- HBV DNA persistently or intermittently ≥ 2000 IU/ml
- Liver biopsy moderate or severe hepatitis and cirrhosis.
<table>
<thead>
<tr>
<th>Phase I</th>
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<td>Immune Clearance</td>
<td>Immune Control</td>
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<th>HBsAg</th>
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<td>HBeAg</td>
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<td>Anti-HBe</td>
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<td>Spontaneous seroconversion to anti-HBe may occur</td>
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<td>ALT</td>
<td>Persistently normal</td>
<td>Persistently or intermittently elevated</td>
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<td>HBV DNA</td>
<td>≥20,000 IU/mL</td>
<td>Persistently or intermittently ≥20,000 IU/mL</td>
<td>&lt;2,000 IU/mL</td>
<td>Persistently or intermittently ≥2,000 IU/mL</td>
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<td>Liver Histology</td>
<td>Normal or mild hepatitis</td>
<td>Moderate - severe hepatitis</td>
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<td>Cirrhosis</td>
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<td>Cirrhosis</td>
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Natural history: disease progression

- The pathogenesis of CHB-associated liver injury is complex:
  - Chronic intrahepatic replication of HBV results in an ongoing cascade of inflammation, injury, and repair.
  - Without resolution, this inflammatory cycle leads to scarring and fibrosis.
  - Ending in cirrhosis and loss of hepatic function.
  - Uncontrolled hepatocyte regeneration with the potential for HCC.
Natural history: disease progression

- HBV-DNA levels are the most important marker of progression.
  - The development of HCC is 10 times greater in patients with persistent HBV DNA >20,000 IU/mL than in those with levels <2,000 IU/mL.
  - Development of cirrhosis is significantly elevated for those with HBV DNA levels as low as 2,000 IU/mL and sixfold greater for those with HBV DNA ≥200,000 IU/mL.

Patients even with ALT levels within the normal range are at risk for the development of cirrhosis and HCC if HBV DNA levels are higher than 2,000 IU/mL.

Natural history: disease progression

ALT Levels

People with slightly increased ALT activity, but still within the normal range, should be closely observed and further investigated for liver diseases.

Natural history: disease progression

- **ALT Levels**

  - Studies show patients with low-normal or high-normal ALT levels (0.5-1 times the upper limit of normal [ULN]) are at risk of developing complications of liver disease.


Natural history: disease progression

- **Other Factors**

  Host and viral risk factors associated with increased rates of cirrhosis and / or HCC include:
  
  - Older age (longer duration of infection)
  - Habitual alcohol consumption
  - Co-infection with hepatitis C virus (HCV), hepatitis D virus (HDV) or human immunodeficiency virus (HIV)
Natural history: disease progression

- Carcinogens such as aflatoxin and tobacco
- Male gender
- Family history of HCC
- History of reversion from anti-HBe to HBeAg
- Presence of cirrhosis
- HBV genotype C
- Core promoter mutation.
Natural History of Hepatitis B

Acute HBV infection
- 90% neonates
- <5% adults

Chronic infection
- 60%

Progressive chronic hepatitis
- Cirrhosis
- Death

Inactive carrier state
- HCC

Lok AS and McMahon BJ. Hepatology 2007;45:507-39
Disease progression: improving outcomes

CHB patients should have

- HBV DNA levels <2,000 IU/mL with
- ALT levels within the normal range.
- Early detection and prolonged, adequate suppression of viral replication should be the practical goal for the management of CHB.

PATIENT EVALUATION
Patient evaluation

- **Diagnosis**
  - HBV infection is confirmed by the detection of hepatitis B surface antigen (HBsAg) or HBV DNA in serum.
  - In addition to patient exposure history,
  - serology can assist in determining whether infections are newly acquired or chronic.
Diagnosis of newly acquired infections requires one of the following:

- HBsAg in a patient shown to be negative within the last 24 months
- HBsAg and high levels of specific IgM to hepatitis B core antigen (HBc IgM) in the absence of prior evidence of HBV infection
- HBV DNA and high levels of specific IgM to hepatitis B core antigen (HBc IgM) in the absence of prior evidence of HBV infection
Patient evaluation

- **Diagnosis of chronic infection requires**: 
  - Detection of HBsAg or HBV DNA (PCR) in the serum of a patient on two occasions at least six months apart.
  - No clinical or laboratory evidence of acute hepatitis B.
Baseline evaluation

The initial evaluation of patients with CHB should include:

A thorough history and physical examination

- With special emphasis on risk factors for co-infection,
- Alcohol use
- Family history of HBV infection and
- Liver cancer.
Baseline evaluation

Laboratory testing and imaging studies:

- Liver function tests, full blood examination, INR
- HBeAg/anti-HBe, HBV DNA (quantitative viral load)
- Test for HBV genotype (if available)
- HCV antibody, hepatitis D virus antibody and antigen, HIV antibody
Baseline evaluation

- Total antibody to hepatitis A virus; vaccinate if no immunity
- Alfa-foetoprotein (FP) and abdominal ultrasound to screen for HCC
- Consider gastroscopy to look for oesophageal varices if clinical, laboratory or imaging evidence of cirrhosis.
- Liver biopsy is strongly recommended prior to initiating antiviral therapy.
CHB TREATMENT GOALS & OBJECTIVES
Treatment Goal

The primary goal is to improve patient survival by preventing or delaying the development of cirrhosis and hepatocellular carcinoma.
The key treatment objectives are:

- HBV DNA suppression (<2,000 IU/mL; PCR undetectable <60 IU/mL)
- HBsAg loss and seroconversion
- HBeAg loss and seroconversion
- Biochemical and histological improvement
CHB: treatment goals & objectives

- Total viral eradication is not possible with currently available therapy.

- The target therefore is to maintain HBV DNA level at <2000 IU/ml.

- Viral suppression decreases necroinflammation, fibrosis and cirrhosis.
HBsAg Clearance:

- Loss of HBsAg and seroconversion to Anti HBs is deemed as complete response.
- Only achievable in:
  - 3% – 8 % after IFN
  - < 5% with oral therapy.
HBeAg Clearance:

- Loss of HBeAg and Seroconversion to Anti HBe deems decreased viral replication.

- Achievable in
  - 10% - 30% receiving IFN
  - Up to 60% after oral therapy.
Patients To treat

- Treatment is always an individual decision.
- Apart from a number of clinical and biochemical factors patients choice is very important.
- A full explanation to the result, aim and outcome is required.
- The treatment decision should be customized. Every case dealt separately.
- Depending on the patients status they should be explained regarding the options and target.
Treatment: Immune tolerance

- **Immune Tolerance**
  - HBeAg +ve
  - High HBV DNA ($\geq 20,000$ IU/mL)
  - Normal ALT

- Consider liver biopsy if age $> 40$ years

- Only to treat if moderate / severe inflammation on biopsy, otherwise no treatment.

- Monitor with HBV DNA and serum ALT every 6 months
Treatment: Immune Clearance

- Immune Clearance
  - HBeAg +ve
  - High HBV DNA ($\geq 20,000$ IU/mL)
  - Elevated ALT

- If serum ALT minimally elevated (1-2×ULN):
  - Consider liver biopsy if age > 40 years
  - Treat if significant hepatic fibrosis (>F$_2$) or moderate to severe inflammation.
Treatment: Immune Clearance

- If serum ALT persistently or intermittently elevated (>2×ULN):
  - Observe 3-6 months for spontaneous HBeAg seroconversion
  - If not occur then consider liver biopsy and treatment.
Treatment: Immune Control

- **Immune Control**
  - HBeAg – ve
  - HBV DNA ≤ 2,000 IU/mL
  - Persistently normal ALT
  - Mild inflammation & no fibrosis on liver biopsy.

- **No treatment is required.**
Treatment: Immune Escape

- **Immune Escape**
  - HBeAg – ve
  - HBV DNA ≥ 2,000 IU/mL

- **If serum ALT minimally elevated (1-2×ULN):**
  - Consider Liver biopsy if > 40 years.
  - Treat if
    - Hepatic fibrosis (> F2) or
    - If clinical signs of advanced disease without biopsy.
Treatment: Immune Escape

- If serum ALT persistently or intermittently elevated (>2×ULN): Moderate to severe chronic hepatitis with active inflammation & variable fibrosis on liver biopsy.

- Consider liver biopsy and treatment
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<tr>
<td><strong>HBeAg Status</strong></td>
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HBV is a deadly but preventable and treatable disease.

Timely identification of the disease is important.

Staging of the patient is important.

Treatment should be directed based on patients stage and individual factors.
THANK YOU