Hepatitis B

Cliff Titcomb MD

AAIM Triennial GI Workshop
October, 2022

hannover re®

Disclaimer/ Copyright Notice

The information provided in this presentation does in no way whatsoever constitute legal, accounting, tax or other professional advice. While Hannover Rückversicherung AG has endeavoured to include in this presentation information it believes to be reliable, complete and up-to-date, the company does not make any representation or warranty, express or implied, as to the accuracy, completeness or updated status of such information. Therefore, in no case whatsoever will Hannover Rückversicherung AG and its affiliate companies be liable to anyone for any decision made or action taken in conjunction with the information in this presentation or for any related damages.

Hepatitis B (HBV) – Basics

- HBV is a DNA virus - member of the Hepadnaviridae family
- Virus structure has several components
  - Surface protein – surface antigen
  - Lipid layer
  - Inner protein core – core antigen
  - Viral polymerase – needed to replicate viral genetic material
  - Viral genome
    - Partially double stranded DNA
- Virus attaches to liver cells and viral genetic material enters the infected cell
- Viral genome is converted to tightly coiled covalently closed circular DNA (cccDNA)
  - Incorporated into the host cell genome
  - Serves as the template for creating new viral particles
  - Unusually stable and able to avoid immune clearance

Hepatitis B (HBV) – Genotypes

- Ten genotypes have been identified – A to J
- Prevalence varies geographically
  - US – types A (35%), B (22%), C (31%) are most common
  - Asia – types B and C
  - Southern Europe, Middle East and India – type D
- Genotype A responds better to interferon therapy
- Genotype C has generally worse outcomes
  - Higher tendency to chronicity
  - Higher level of viral DNA and rate of positivity of e antigen
  - Higher risk of cirrhosis or cancer

Hepatitis B – Epidemiology

- Estimated 2 billion individuals have been infected worldwide
  - 257 million chronically infected
  - 10-30 million new infections per year
  - 887,000 deaths in 2015
  - Risk of chronic infection varies by geographic area
    - Sub-Sahara Africa – 8.83%
    - Western Pacific region – 5.26%
    - Eastern Mediterranean region – 3.01%
    - Europe – 2.06%
    - Southeast Asia – 1.90%
    - Americas – 0.81%
- Majority of infections in endemic areas occur in the perinatal period or early in childhood

Hepatitis B – Epidemiology

- Estimated 12 million individuals have been infected in the US
  - 800,000 to 2.2 million chronically infected
  - Up to 40,000 new infections may occur per year
  - 3,000 deaths per year
- Foreign born individuals account for 95% of the cases in the US
  - Majority of those chronically infected are of Asian/Pacific Island descent
- Highest incidence rate (new infections) is in those aged 30-39
- Rate of acute hepatitis B has decreased 88.5% since advent of universal vaccination

Hepatitis B – Infectivity and Transmission

- Hepatitis B is extremely infectious with easy transmission
- Virus can survive on inanimate surfaces for up to 7 days
- Modes of transmission
  - Parenteral
    - IV drug use
    - Exposure to blood through medical procedures (needle stick, surgery, dialysis etc.)
  - Non-medical contact with blood
    - Dental procedure, tattooing, sharing razors
  - Sexual contact
    - Heterosexual
    - MSM contact
  - Contact with body fluids
    - Peripartum
    - Daycare centers
    - Household contacts
    - Developmentally disabled (group homes etc.)

Hepatitis B – Prevention

- Vaccine is available and highly effective
  - Leads to the development of HBsAb without the HBcAb
- Universal vaccination of children is recommended
  - First dose at birth
- Children born to HBsAg mothers receive special therapy
  - Vaccination and hepatitis B immune globulin (HBIG) at birth
  - Mothers with high HBV DNA load (> 200,000 IU/ml) are also treated with tenofovir beginning at 28-32 weeks gestation until 1 to 3 months post partum
- Vaccination recommended for high risk adults including:
  - Health care workers
  - IV drug users
  - Individuals with high risk sex behaviors
  - Household contacts of infected individuals
  - Workers in chronic care facilities
  - Travelers to high risk areas

Hepatitis B – Serology

- Hepatitis B surface antigen (HBsAg)
  - Protein from the viral coat
  - Indicates active infection and potential infectivity
  - Often produced in excess of the number of actual viral particles
  - High levels may cause immune fatigue or tolerance in the host

- Antibody to the core protein of the virus particle (HBcAb)
  - Found only in those with a prior hepatitis B infection
  - All of those infected will develop this antibody
  - Two types
    - IgM – only found associated with recent acute infection
    - IgG – found associated with recent or remote infections, may persist for life
    - Latter may be the only marker for a prior acute infection

Hepatitis B – Serology

- Hepatitis B surface antibody (HBsAb)
  - Develops with recovery from acute infection or after vaccination
    - Presence of a positive HBcAb indicates prior infection
    - Presence of the HBsAb alone indicates vaccination
  - Only 80% of those who recover from and acute infection develop the HBsAb
  - Conveys immunity from reinfection with the virus
  - Does *NOT* indicate cure or freedom from potential reactivation of the virus in those that have been infected

- Hepatitis B e antigen (HBeAg)
  - Protein that is an indicator of active viral replication
  - Important prognostic marker
  - Individuals with a Pre-Core mutation do not develop the e antigen
    - Viral DNA level determines degree of viral replication and infectivity in these cases

Hepatitis B – Serology

- Antibody to the hepatitis B e antigen (HbeAb)
  - Indicates seroconversion or cessation of active viral replication
  - Appearance is a good prognostic marker and goal of initial therapy

- Viral DNA (HBV DNA)
  - Gold standard for presence of the virus in the blood, viral replication & infectivity
  - Level represents a measure of active replication even if e antigen not present
  - Level has prognostic value

Hepatitis B – Sequence of Events in a Resolved Infection

- Incubation period to onset of clinical illness is approximately 45 to 160 days
- Viral DNA is detected first (10 – 20 days before the surface antigen)
  - Usually disappears some time after e antigen becomes undetectable
- HBsAg appears 1 – 9 weeks after infection (average 4 weeks)
  - Persists for several months
- HbeAg is detectable shortly thereafter and persists for 3 to 6 weeks
- HbcAb appears shortly before the onset of clinical illness
  - IgM version persists for several months, then disappears
  - IgG version continues indefinitely
- HBeAb appears shortly after the e antigen disappears
- HBsAb appears after the surface antigen is no longer detectable
  - May be a gap when the surface antigen and surface antibody are both negative
  - Infection detected by IgM core antibody or presence of viral DNA

Hepatitis B – Serologic Screening (HBsAg and/or HBcAb)

- Individuals from a country with a prevalence ≥ 2%
- US born, not vaccinated, with parents from an area with prevalence ≥ 8%
- History of high risk sexual activities
- Those being treated for a sexually transmitted disease
- History of IV drug use
- Unexplained ALT elevation
- All pregnant women
- Persons needing immunosuppressive or chemotherapy or dialysis
- Persons with other chronic liver disease
- Persons with HIV disease or hepatitis C infection
- Household contacts of someone who is chronically infected
- Health care or other workers regularly in contact with bodily fluids
- Blood, organ or sperm donors

Key Point to Remember

- Hepatitis B virus is NOT cytopathic
  - Virus does not injure liver cells directly
- Damage is done by the immune response to the infection
- Elevated liver function tests, especially ALT reflect the injury and, indirectly, viral activity

Hepatitis B – Acute Disease

- Clinical findings depend on host factors
  - Infants, children under age 5 and immunosuppressed individuals are usually asymptomatic
  - Older children and adults – symptomatic in 30%-50% of cases
- Symptoms include jaundice, anorexia, nausea, vomiting, hepatomegaly, fever
- Fulminant hepatitis is possible but uncommon
- Mortality rate from acute hepatitis B is < 1.5%
  - Primarily in adults > age 55
- Loss of the surface antigen and development of the surface antibody indicates clinical resolution, immunity from reinfection and *functional* cure
- However, viral ccc DNA remains in the nucleus of the infected cells for life
  - May become reactivated with immune suppression or cancer chemotherapy

Hepatitis B – Chronic Disease

- Defined as persistence of HBsAg beyond 6 months post infection
- Probability of chronic infection depends on the age of onset of disease
  - Perinatal infection – 90%
  - Infection in childhood (before age 5) 30%-50%
  - Adult - < 5%
- A significant number of chronically infected individuals will die prematurely
  - 25% of those infected during childhood
  - 15% of those developing chronic disease after childhood
- Major causes of death
  - Hepatocellular cancer (HCC) – second most common cause of cancer death worldwide
    - Develops in 30% of those with cirrhosis
    - Approximately 10% of cases occur in individuals without cirrhosis
  - Cirrhosis of the liver
    - Develops in up to 40% of untreated patients

Chronic Disease – Different Phases

- Immune tolerant phase
  - Primarily occurs with infection at birth
  - More common with genotype C
  - Associated with a positive e antigen
  - Seroconversion to e antibody may or may not occur and timing varies with genotype
  - HBV DNA $\geq$ 200,000 IU/ml, often in the millions
  - ALT normal
  - No or minimal inflammation or fibrosis on biopsy

Chronic Disease – Different Phases

- Immune active phase
  - Phase of active virus clearance
  - ALT levels are elevated and reflect immune damage to the hepatocytes
  - HBV DNA usually ≥ 20,000 IU/ml
  - High risk of cirrhosis and HCC
  - Seroconversion from e antigen to e antibody may occur
    - 10% to 40% revert to e antigen positive, often with a flare of hepatitis
    - 20% remain in immune active phase
    - Remainder go to Inactive Phase

Chronic Disease – Different Phases

- Inactive phase
  - E antigen negative
  - ALT normal
  - HBV DNA < 2,000 IU/ml, often undetectable
  - Liver inflammation improves over time
  - Fibrosis may revert over time
    - May only slowly change on biopsy
  - 20% may revert to immune active phase with recurrent liver damage
    - Remain at risk for cirrhosis and HCC
  - About 1%-2% per year will clear the surface antigen
    - Clearance is variable and unpredictable
    - May or may not develop the surface antibody

Hepatitis B – Mutations that Affect Prognosis

- Basal Core Promoter (BCP)
  - Associated with increased risk of HCC and cirrhosis
  - Relative risk 1.7-3.2 for HCC
  - RR – 1.9 for cirrhosis

- Pre-Core (PC)
  - Prevents the production of the e antigen
  - Common in the Mediterranean region
  - Does not occur with genotype A
  - Tip off is the presence of high viral DNA level with absent e antigen
    - In this scenario prognosis is driven by the viral load
  - More common in individuals with active liver inflammation
  - Some variants may be associated with an increased risk of HCC
  - Risk of cirrhosis appears to be lower

Risk Factors for Developing Cirrrhosis or HCC

- E antigen positive
- Higher HBV DNA/viral load
- Elevated ALT level, especially higher values
- Genotypes C and F
- Basal core promoter (BCP) mutation
- Co-infection with other viruses (hepatitis C, D or HIV)
- Male sex (3 to 4:1 risk)
  - Higher for HCC than cirrhosis
- Age – increases significantly after 40
- Family history of cirrhosis or HCC
- Moderate to heavy alcohol use
- Smoking
- Coffee intake decreases risk

Hepatitis B – Goals of Therapy

- Suppression of inflammation
- Reduction or prevention of liver fibrosis
- Avoidance of cirrhosis
- Prevention of hepatocellular cancer
- For those who achieve goals about 1% to at most 2% become HBsAg negative per year
- Loss of HBsAg = “Functional Cure”

Hepatitis B – When to Treat

- Most treatment occurs in immune active phase
  - ALT elevation, generally more than 2x normal (levels may be variable) *plus*
  - E antigen positive with HBV DNA levels > 20,000 IU/ml *or*
  - E antibody positive with HBV DNA levels > 2,000 IU/ml *or*
  - Liver biopsy or noninvasive tests showing moderate to severe inflammation and/or fibrosis

- Clear reactivation after seroconversion also treated
  - Return to positive HBeAg and/or increased HBV DNA levels
  - Rebound of ALT elevations

Hepatitis B – When to Treat

- Immune tolerance phase generally not treated
  - High viral load (> 20,000 IU/ml), e antigen positive, normal ALT
  - Viral clearance only 10% with therapy
  - Exceptions based on liver biopsy or non-invasive testing results:
    - Moderate to severe inflammation (A2, A3) and/or
    - Moderate or greater fibrosis (≥ F2)
  - May be most useful in those > age 40

- No evidence of benefit in the truly inactive carrier phase
  - E antigen negative, e antibody positive
  - HBV DNA < 2000 IU/ml or undetectable
  - Persistently normal ALT levels
  - No biopsy or noninvasive evidence for significant inflammation or fibrosis

Hepatitis B – 2 Major Types of Treatment

- Interferon alfa (peg-interferon)

- Nucleos(t)ide analogs
  - Entecavir (Baraclude)
  - Tenofovir disoproxil (Viread)
  - Tenofovir alafenamide (Vemlidy)
  - Lamivudine (Epivir)
  - Adefovir (Hepsera)

Hepatitis B – Interferon Therapy

- Advantages
  - Limited duration of therapy (up to 12 months)
  - No viral resistance
  - Immunomodulatory and modest antiviral effects
  - Greater chance of clearing hepatitis B surface antigen

- Disadvantages
  - Requires subcutaneous injection
  - Can’t be used in decompensated cirrhosis
  - Frequent side effects – often difficult to tolerate

Hepatitis B – Nucleos(t)ide analogs

- Advantages
  - Oral use
  - Strong antiviral activity
  - Side effects are infrequent (lowest with tenofovir alafenamide or Vemlidy)
  - Can use in compensated and de-compensated cirrhosis

- Disadvantages
  - Drug resistance can occur, affects other drugs in the class
    - Especially lamivudine (Epivir) and adefovir (Hepsera)
    - Entecavir and tenofovir are the drugs of first choice because of low resistance
  - Needs to be used for an extended period of time- often lifetime
    - Compliance and side effects may become an issue
  - Consideration for stopping drugs in those who do not achieve HBsAg loss
    - After 1 year in those with HBeAg loss
    - After 3 years in those who were HBeAg negative at time of therapy
  - Relapses may occur after drug is stopped

Hepatitis B – Indicators for Success of Therapy

- Decrease of HBV DNA values to undetectable levels
- Seroconversion of HBeAg to HBeAb
- Normalization of serum ALT readings
- For those who achieve goals about 1% to 2% become HBsAg negative per year
- Loss of HBsAg = “Functional Cure”

Hepatitis B – "Functional" Cure

- Clearance of surface antigen
  - With or without development of the surface antibody
- Risk of cirrhosis remains very low
- Risk of HCC is reduced but remains elevated relative to the general population
  - Risk of HCC and reactivation persists due to presence of the ccc DNA in the cells
- All individuals who are going to receive immunosuppressive or chemotherapy should be checked for a prior HBV infection
  - Treatment may cause reactivation of the virus
  - Even those with a “Functional” cure
    - Occurs in 1.5% to 23.8% of cases

Hepatitis B – New Therapies in Development

- Drugs that reduce HBsAg levels
  - Fight immune fatigue
- Entry inhibitors
  - Impair viral entry into cells
- Capsid inhibitors
  - Impair viral particle assembly
- Molecular therapies
  - CRISPR/Cas9
    - Search out and destroy cccDNA
  - RNA inhibitors
    - Impair viral RNA products
    - Effectively silence viral genome

Hepatitis B – "True" Cure

- Involves elimination of the cccDNA
- Will likely require combination therapy
- Similar to approach with HIV disease
- At present effective, reliable therapy is not available

hannover re®